

## **EXHIBIT B**

### **Guidelines for the diagnosis and treatment of chronic heart failure**

## Task Force Report

# Guidelines for the diagnosis and treatment of chronic heart failure

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## Diagnosis of chronic heart failure

### Introduction

#### Methodology

These Guidelines are based on the Diagnostic and Therapeutic Guidelines published in 1995 and 1997<sup>[1,2]</sup>, respectively, and have now been combined into one paper. Where new information is available an update has been performed while other parts are unchanged or adjusted to a limited extent.

The aim of this report is to provide practical guidelines for the diagnosis, assessment and treatment of heart failure for use in clinical practice and in addition for epidemiological surveys and clinical trials. They are intended as a support for practising physicians and other health care professionals concerned with the management of heart failure patients and provide advice on how to manage these patients including recommendations for referral. The recommendations in these guidelines should always be considered in the light of local regulatory requirements for the administration of any chosen drug or device.

This report was drafted by a Task Force (see Appendix 1) appointed by the Committee for Practice Guidelines and Policy Conferences of the European Society of Cardiology (ESC). It was circulated among the Nucleus of the Working Group on Heart Failure, other Working Groups, and several experts in the field of heart failure. It was updated based on comments received. It was then sent to the Committee and after their input the document was approved for publication.

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#### LEVEL OF EVIDENCE

Recommendations regarding treatments have been based on the degree of available evidence.

Level of evidence	Available evidence
A	At least two randomized trials supporting recommendation
B	One randomized trial and/or meta-analysis supporting recommendation
C	Consensus statement from experts based on trials and clinical experience

Major conclusions or recommendations have been highlighted by bullets.

### Epidemiology

- Much is now known about the epidemiology of heart failure in Europe, but the presentation and aetiology are heterogeneous and less is known about differences between countries.

Estimates of the prevalence of symptomatic heart failure in the general European population range from 0.4% to 2%<sup>[3]</sup>. The prevalence of heart failure increases rapidly with age<sup>[4]</sup>, with the mean age of the heart failure population being 74 years. As the proportion of the population that is elderly is increasing, this partly accounts for the rising prevalence of heart failure<sup>[5–7]</sup>. Unlike other common cardiovascular diseases, the age-adjusted mortality attributed to heart failure also appears to be increasing. The European Society of Cardiology represents countries with a total population of over 900 million, suggesting that there are at least 10 million patients with heart failure in those countries. There are also patients with myocardial dysfunction

without symptoms of heart failure and who constitute approximately a similar prevalence<sup>[8,9]</sup>. The prognosis of heart failure is uniformly poor if the underlying problem cannot be rectified. Half of patients carrying a diagnosis of heart failure will die within 4 years and in patients with severe heart failure more than 50% will die within 1 year<sup>[5,7]</sup>. Recent studies have confirmed the poor long-term prognosis<sup>[10,11]</sup> in patients with asymptomatic myocardial dysfunction<sup>[12]</sup>. No temporal improvement over time has been found in community reports from the Framingham study<sup>[6]</sup> or Rochester project<sup>[11]</sup>. In contrast, a Scottish report provides survival rates after hospital discharge from 1986 to 1995 suggesting improved prognosis over time<sup>[13]</sup>.

Recent studies show that the accuracy of diagnosis by clinical means alone is often inadequate<sup>[14,15]</sup> particularly in women, the elderly and the obese. In order to study properly the epidemiology and prognosis and to optimize the treatment of heart failure the uncertainty relating to the diagnosis must be minimized or avoided.

### *Descriptive terms in heart failure*

#### *Acute vs chronic heart failure*

Chronic heart failure, often punctuated by acute exacerbations, is the most common form of heart failure. A definition of chronic heart failure is given below.

The term acute heart failure is often used, exclusively, to mean acute (cardiogenic) dyspnoea characterized by signs of pulmonary congestion including pulmonary oedema. However, acute heart failure could also apply to cardiogenic shock, a syndrome characterized by a low arterial pressure, oliguria and a cool periphery, that needs to be distinguished from pulmonary oedema. It is advisable not to use the term acute heart failure but the more precise terms acute pulmonary oedema or, where applicable, cardiogenic shock.

#### *Systolic vs diastolic heart failure*

As ischaemic heart disease is the commonest cause of heart failure in industrialized societies most heart failure is associated with evidence of left ventricular systolic dysfunction, although diastolic impairment at rest is a common if not universal accompaniment. Diastolic heart failure is often presumed to be present when symptoms and signs of heart failure occur in the presence of a preserved left ventricular systolic function (normal ejection fraction/normal end-diastolic volume) at rest. Predominant diastolic dysfunction is relatively uncommon in younger patients, but increases in importance in the elderly, in whom systolic hypertension, myocardial hypertrophy are contributors to cardiac dysfunction. Most patients with heart failure and impairment of diastolic function also have impaired systolic function.

#### *Other descriptive terms in heart failure*

Right and left heart failure refer to syndromes presenting predominantly with congestion of the systemic or

**Table 1 Definition of heart failure. Criteria 1 and 2 should be fulfilled in all cases**

- |  |     |
|--|-----|
| 1. Symptoms of heart failure<br>(at rest or during exercise) | and |
| 2. Objective evidence of cardiac dysfunction<br>(at rest)    | and |
| (in cases where the diagnosis is in doubt)                   |     |
| 3. Response to treatment directed towards heart failure      |     |

pulmonary veins, respectively. The terms do not necessarily indicate which ventricle is most severely damaged. High and low-output, forward and backward, overt, treated, congestive and undulating are other descriptive terms still in occasional use; the clinical utility of these terms have yet to be determined.

Mild, moderate or severe heart failure is used as a clinical symptomatic description where mild is used for patients who can move around with no important limitations, severe for patients who are markedly symptomatic and need frequent medical attention and moderate for the remaining patient cohort.

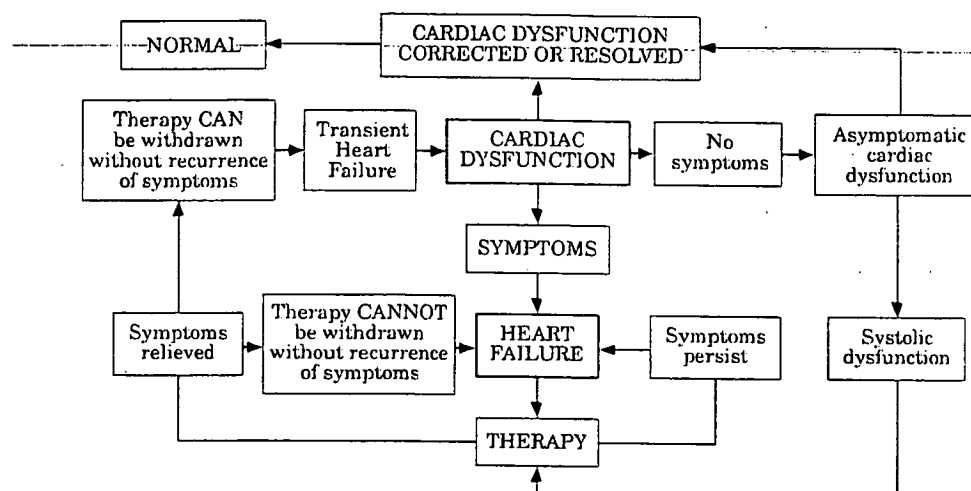
Clinical syndromes are caused by an abnormality of the heart and recognized by a characteristic pattern of cardiac and extra-cardiac responses, including those of haemodynamic, renal, neural and hormonal nature.

#### *Definition of chronic heart failure*

Many definitions of chronic heart failure exist<sup>[16-19]</sup> but highlight only selective features of this complex syndrome. None is entirely satisfactory and one commonly used definition is: heart failure is a pathophysiological state in which an abnormality of cardiac function is responsible for the failure of the heart to pump blood at a rate commensurate with the requirements of the metabolizing tissues.

A simple objective definition of chronic heart failure is currently impossible as there is no cut-off value or cardiac or ventricular dysfunction or change in flow, pressure, dimension or volume that can be used reliably to identify patients with heart failure. The diagnosis of heart failure relies on clinical judgement based on a history, physical examination and appropriate investigations.

The Task Force considers the essential components of heart failure to be a syndrome where the patients should have the following features; symptoms of heart failure, typically breathlessness or fatigue, either at rest or during exertion, or ankle swelling and objective evidence of cardiac dysfunction at rest (Table 1). A clinical response to treatment directed at heart failure alone is not sufficient for diagnosis, although the patient should generally demonstrate some improvement in symptoms and/or signs in response to those treatments where a relatively fast symptomatic improvement could be anticipated e.g. diuretic or nitrate administration. It should also be recognized that treatment may obscure



**Figure 1** Relationship between cardiac dysfunction, heart failure and heart failure rendered asymptomatic.

a diagnosis of heart failure by relieving the patient's symptoms. Therapy should not usually be initiated until a diagnosis of chronic heart failure has been established with reasonable certainty.

The distinctions between cardiac dysfunction, persistent heart failure, heart failure that has been rendered asymptomatic by therapy and transient heart failure are outlined in Fig. 1. It is important to note that exercise-induced ventricular dysfunction, usually due to myocardial ischaemia, may cause a rise in ventricular filling pressure and a fall in cardiac output and induce symptoms of heart failure such as breathlessness. However, as both the underlying pathophysiology and the treatment of this condition is generally different from that of heart failure secondary to chronic ventricular dysfunction, such patients should not be diagnosed as having chronic heart failure.

### *Aetiology of heart failure in Europe*

- Heart failure should never be the final diagnosis.

The aetiology of heart failure and the presence of exacerbating factors or other diseases that may have an important influence on management should be carefully considered in all cases. The extent to which the cause of heart failure should be pursued by further investigation will depend on the resources available and the likelihood that diagnosis will influence management.

Chronic heart failure may be due to myocardial dysfunction, arrhythmias, valve abnormalities, pericardial disease or induced by rhythm disturbances. Anaemia, renal or thyroid dysfunction and cardio-depressant drugs may exacerbate, or more rarely cause, heart failure. Acute pulmonary oedema and cardiogenic shock have an aetiological spectrum similar to chronic heart failure, though pulmonary oedema is rarely due to pericardial disease. Standard cardiology textbooks should be consulted for a more extensive list of the

causes of heart failure. In Europe, myocardial dysfunction secondary to coronary artery disease, usually as a consequence of myocardial infarction, is the most common cause of heart failure among patients under 75 years of age<sup>[20]</sup> and clear abnormalities in systolic function are usually present. Among elderly patients, who are often less intensively investigated, an accurate diagnosis of the presence and aetiology of heart failure is more difficult and obscured by multiple other diagnoses. Systolic hypertension and cardiac hypertrophy, cell loss and fibrosis may be more important causes of heart failure in the elderly and may be more likely to manifest predominantly as abnormalities of diastolic function. The aetiology of heart failure will also depend on ethnic origin, socioeconomic status and geographic location. Several background factors can also induce heart failure e.g. hypertension, coronary artery disease and valvular abnormalities.

### *Importance of identifying potentially reversible exacerbating factors*

Symptoms of chronic heart failure, pulmonary oedema and shock may be caused by tachy- and bradyarrhythmias or myocardial ischaemia even in patients without major, permanent cardiac dysfunction. Myocardial ischaemia, changes in valvular regurgitation, pulmonary embolism, infection, arrhythmia or renal dysfunction, side effects of drug therapy and excessive fluid, sodium or alcohol intake may all cause or exacerbate symptoms and/or signs of heart failure in patients with pre-existing cardiac dysfunction. It is important to identify any reversible factors in order to treat heart failure optimally.

### *Importance of the holistic approach to the diagnosis of heart failure*

A proper diagnostic formulation must extend beyond the cardiac problem, particularly in the elderly

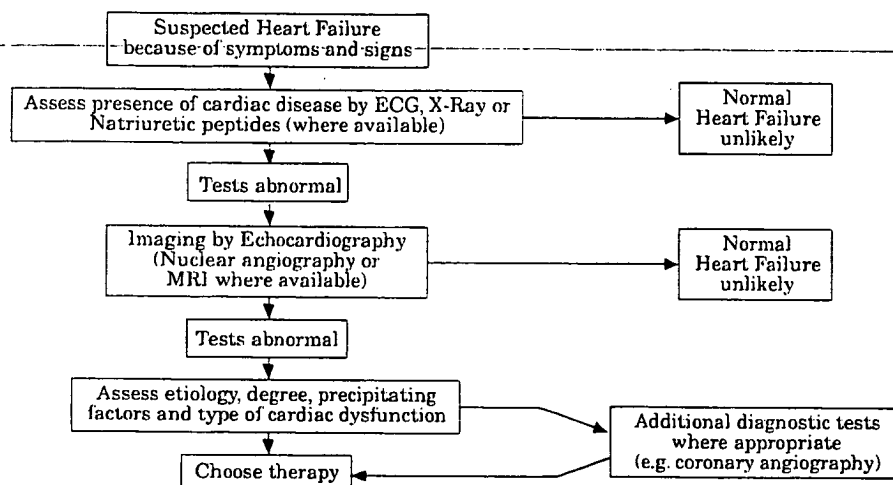


Figure 2 Algorithm for the diagnosis of heart failure.

population in whom multiple rather than single diseases are common. Disease of the peripheral vasculature<sup>[21]</sup> and other organs including the kidney and lungs may have an important influence on diagnosis and the choice of treatment. For instance, in patients with prostatic hypertrophy a vigorous diuresis may precipitate acute urinary retention.

### *Aspects of the pathophysiology of the symptoms of heart failure relevant to diagnosis*

The origin of the symptoms of heart failure are not fully understood. Increased pulmonary capillary pressure is undoubtedly responsible for pulmonary oedema in part, but studies conducted during exercise in patients with chronic heart failure demonstrate no simple relationship between capillary pressure and exercise performance<sup>[22,23]</sup>. This suggests either that raised pulmonary capillary pressure is not the only factor responsible for exertional breathlessness or that current techniques to measure true pulmonary capillary pressure may not be adequate. In this context variation in the degree of mitral regurgitation will influence breathlessness. Abnormalities of pulmonary diffusion, peripheral or respiratory skeletal muscle<sup>[24]</sup>, general cardiovascular deconditioning or overweight<sup>[25,26]</sup> may also contribute importantly to the sensation of breathlessness. Fatigue is another essential symptom in heart failure. The origins of fatigue are even more obscure and compounded by difficulties in quantifying this symptom<sup>[27]</sup>. Peripheral oedema is poorly related to right heart pressures; capillary permeability for fluid and small proteins and reduced physical activity being important additional factors. Extracardiac causes of oedema not related to heart failure are common.

Although impairment of cardiac function is central to the development of heart failure, altered peripheral

blood flow, especially to the kidney and skeletal muscle, is typical and probably of major pathophysiological importance<sup>[28]</sup>. Similarly, activation of a number of neuroendocrine systems is characteristic of heart failure<sup>[29,30]</sup>. Baroreceptor dysfunction is an important link between vasomotor and neuroendocrine dysfunction<sup>[31]</sup>. Understanding chronic heart failure has moved from a haemodynamic concept into accepting the importance of neuroendocrine pathophysiological changes in the progression as well as for the treatment of heart failure<sup>[32]</sup>. Activation of various cytokines may also contribute to cardiac dysfunction and to the clinical syndrome, particularly in more advanced stages<sup>[33]</sup>.

### *Possible methods for the diagnosis of heart failure in clinical practice*

#### *Symptoms and signs in the diagnosis of heart failure*

- Symptoms and signs are important as they alert the observer to the possibility that heart failure exists. The clinical suspicion of heart failure must be confirmed by more objective tests, particularly aimed at assessing cardiac function (Fig. 2).

Breathlessness, ankle swelling and fatigue are the characteristic symptoms of heart failure, but may be difficult to interpret, particularly among elderly patients, the obese and in women. Inter-observer agreement on the presence or absence of symptoms of heart failure may be low<sup>[34]</sup> notably in the days following a myocardial infarction. There is no standard questionnaire available for the diagnosis of heart failure. In the context of clinical or epidemiological studies, several scoring systems are available that await proper validation and cannot be recommended for clinical practice at present<sup>[35]</sup>.

Peripheral oedema, a raised venous pressure and hepatomegaly are the characteristic signs of congestion

of systemic veins<sup>[36,37]</sup>. Clinical signs of heart failure should be assessed in a careful clinical examination including observing, palpating and auscultating the patient. Unfortunately, clinical examination is often replaced by laboratory investigations which reduce the experience in bedside medicine among physicians. Peripheral oedema and hepatomegaly have low positive predictive value, while determination of the jugular venous pressure may be difficult. Peripheral oedema is usually absent in well-treated heart failure and primarily left ventricular dysfunction, even if severe<sup>[37]</sup>. Although cardiologists attain high agreement on the presence of elevated jugular venous pressure under study conditions, the reproducibility is much lower among non-specialists<sup>[36]</sup>. Moreover, many patients, even with well documented heart failure, even if severe, do not have an elevated jugular venous pressure<sup>[37]</sup>. Tachycardia is non-specific and may be absent even in severe heart failure, particularly in the presence of beta-blocker therapy<sup>[37]</sup>. Other signs of heart failure require considerable expertise for their detection. A third heart sound is usually considered to be present in patients with severe heart failure<sup>[37]</sup>, but is not specific to heart failure<sup>[38]</sup>. Although cardiology specialists may attain high agreement for the presence of a third heart sound under study conditions<sup>[36]</sup> the inter-observer agreement is less than 50% among non-specialists<sup>[39]</sup> and probably even lower in clinical practice. Pulmonary crepitations also have low positive predictive value and inter-observer differences in eliciting this sign are high<sup>[40]</sup>. When cardiac murmurs are present their origin and role in the symptomatology should be identified.

When multiple signs of heart failure are present, including a displaced apex beat, pitting oedema, a raised venous pressure and when a third heart sound is heard confidently then, in the presence of appropriate symptoms, a clinical diagnosis of heart failure may be made with some confidence. Although a clinical diagnosis reached in this way may be specific it will fail to identify many patients who might benefit from treatment. The subjective component of the examination and the inability to make a permanent direct record are further weaknesses of a diagnosis made on clinical features alone.

#### *Symptoms and the severity of heart failure*

- There is a poor relationship between symptoms and the severity of cardiac dysfunction<sup>[15,35]</sup> and between symptoms and prognosis<sup>[41]</sup>.

Once a diagnosis of heart failure has been established symptoms may be used to classify the severity of heart failure and should be used to monitor the effects of therapy. The New York Heart Association classification (NYHA) is in widespread use (Table 2). The use of examples such as walking distance or number of stairs climbed is recommended. In other situations, the classification of symptoms into mild, moderate or severe is used. Patients in NYHA class I would have to have objective evidence of cardiac dysfunction, have a past

**Table 2 New York Heart Association Classification of Heart Failure**

Class I.	No limitation: ordinary physical exercise does not cause undue fatigue, dyspnoea or palpitations.
Class II.	Slight limitation of physical activity: comfortable at rest but ordinary activity results in fatigue, palpitations or dyspnoea.
Class III.	Marked limitation of physical activity: comfortable at rest but less than ordinary activity results in symptoms.
Class IV.	Unable to carry out any physical activity without discomfort: symptoms of heart failure are present even at rest with increased discomfort with any physical activity.

history of heart failure symptoms and be receiving treatment for heart failure in order to fulfil the basic definition of heart failure.

In acute myocardial infarction, the classification described by Killip has been used<sup>[42]</sup>. The value of questionnaires for the measurement of quality of life in the context of classification of severity is still being debated. The most frequently used questionnaire is the Minnesota Living With Heart Failure<sup>[43]</sup>. It is important to realize the common dissociation between symptoms and myocardial dysfunction. The severity of symptoms are highly dependent on the efficacy of therapy, patient expectation and medical interpretation. Mild symptoms should not be equated with minor cardiac dysfunction.

#### *Electrocardiogram*

- A normal ECG suggests that the diagnosis of chronic heart failure should be carefully reviewed.

Electrocardiographic changes in patients with heart failure are frequent. The negative predictive value of a normal ECG to exclude left ventricular systolic dysfunction exceeds 90%<sup>[44-47]</sup>. On the other hand, the presence of anterior Q waves and a left bundle branch block in patients with ischaemic heart disease are good predictors of a decreased ejection fraction<sup>[44]</sup>. ECG signs of left atrial overload or left ventricular hypertrophy may be associated with systolic as well as isolated diastolic dysfunction, but they have a low predictive value. The ECG is crucial for detecting atrial fibrillation or flutter and sometimes ventricular arrhythmia as causative or contributing factors for heart failure. The diagnostic contribution of ECG anomalies markedly increases if clinical symptoms and signs of heart failure co-exist. ECG recordings do not need to be repeated in the absence of changes of clinical status.

#### *The chest X-ray*

- Chest X-ray should be part of the initial diagnostic work-up in heart failure.

A high predictive value of X-ray findings is only achieved by interpreting the X-ray in the context of clinical findings and ECG anomalies<sup>[45]</sup>. The investigation is useful to detect the presence of cardiac enlargement and pulmonary congestion<sup>[48-51]</sup>. Cardiomegaly is

**Table 3 Renal function estimated by a modified creatinine clearance according to Cockcroft and Gault<sup>[22]</sup>. Values should be reduced by 15% for women**

$$\text{Creatinine clearance} = (140 - \text{age}) \times \text{weight (kg)} \times 1.22 / \text{S-creatinine (umol} \times 10^{-3})$$

frequently absent in patients with acute heart failure and also in cases with diastolic dysfunction. In patients with chronic heart failure, however, an increased cardiac size, as judged by a cardiothoracic ratio >0.50, and the presence of pulmonary venous congestion are useful indicators of abnormal cardiac function with a decreased ejection fraction and/or elevated left ventricular filling pressure<sup>[52]</sup>. Interstitial and alveolar pulmonary oedema are also reliable and important signs of severe left ventricular dysfunction<sup>[53]</sup>. However, in individual patients the radiographic findings alone do not allow a reliable estimation of the pulmonary capillary pressure and are therefore not suitable as the only basis for therapeutic decisions<sup>[54]</sup>. There may also be inter-observer variations in the interpretation of chest X-ray changes<sup>[55,56]</sup>. The relationship between radiological signs and haemodynamic findings may depend on the duration as well as the severity of cardiac dysfunction<sup>[57]</sup>.

#### Haematology and biochemistry

- The following laboratory investigations are recommended as part of a routine diagnostic evaluation of patients with chronic heart failure: Complete blood count (Hb, leukocytes, platelets), S-electrolytes, S-creatinine, S-glucose, S-hepatic enzymes and urinalysis. Additional tests to consider include: C-reactive protein (CRP), thyroid stimulating hormone (TSH), S-uric acid and S-urea. In acute exacerbations it is important to exclude acute myocardial infarction by myocardial specific enzyme analysis.

Anaemia may exacerbate pre-existing heart failure. A raised haematocrit suggests that breathlessness may be due to pulmonary disease, cyanotic congenital heart disease or a pulmonary arteriovenous malformation.

Elevated serum creatinine can also be caused by primary renal disease, which may induce all the features of heart failure by volume overload. Heart failure and renal dysfunction often coincide because of the underlying diseases, such as diabetes and hypertension, or as a consequence of impaired kidney perfusion by reduction in cardiac output. Further, age alone can be a cause of reduced creatinine clearance. For calculation of creatinine clearance, see Table 3. Excessive treatment with diuretics and/or ACE-inhibitors, sometimes together with potassium-sparing diuretics, are other reasons for a high s-creatinine value. Concomitant administration of ACE inhibition and potassium-sparing diuretics may lead to hyperkalaemia. Untreated heart failure is rarely associated with major electrolyte disturbances, but they are quite common in patients on

diuretics. Liver enzymes may be elevated by hepatic congestion.

Urine analysis is useful in detecting proteinuria and glycosuria, alerting the clinician to the possibility of underlying renal problems or diabetes mellitus, conditions that may contribute to or complicate heart failure.

Heart failure due to thyrotoxicosis is frequently associated with rapid atrial fibrillation which may be the presenting feature of thyrotoxicosis in the elderly. Hypothyroidism may also present as heart failure.

Hyponatraemia and renal dysfunction in the setting of heart failure indicate a bad prognosis.

#### Echocardiography

- As objective evidence of cardiac dysfunction at rest is necessary for the diagnosis of heart failure, echocardiography is the preferred method for this documentation.

The access to and use of echocardiography is encouraged for the diagnosis of heart failure. Transthoracic Doppler echocardiography is rapid, safe and widely available. It allows the assessment of chamber dimensions, wall thicknesses and geometry, indices of regional, global, systolic and diastolic ventricular function. The most important parameter of ventricular function for identifying patients with cardiac systolic dysfunction and those with preserved systolic function is the left ventricular ejection fraction. Echocardiography also provides rapid and semi-quantitative assessment of valvular function, especially of mitral, tricuspid and aortic stenosis and regurgitation and grading of mitral regurgitation. The degree of secondary tricuspid regurgitation gives an estimate of pulmonary artery pressures.

Although M-mode measurements benefit from high temporal resolution, they are inaccurate in patients with spherical ventricles and regional dysfunction. The apical biplane summation of discs method — modified Simpson method — is validated<sup>[58]</sup> but relies on accurate endocardial definition. Although quantitative visual assessment has been shown to detect low left ventricular ejection fraction with good sensitivity and specificity, this procedure is only reliable with experienced observers. Other measurements include: fractional shortening, sphericity index, atrioventricular plane displacement<sup>[59]</sup>, myocardial performance index<sup>[60]</sup>, and left ventricular wall motion index<sup>[61]</sup>. Although 'eyeball' grading of left ventricular systolic dysfunction into mild, moderate or severe categories is widely used in clinical practice, clearly, standardization among different observers is difficult to obtain<sup>[62]</sup>. The interpretation of ejection fraction shortly after an acute myocardial infarction or in the context of a mitral insufficiency is more uncertain.

Reproducibility of ejection fraction among different observers is poor even when the same techniques are used. Preserved left ventricular systolic function, however, usually implies a resting baseline left ventricular ejection fraction of  $\geq 40$ –45%, normal or, in the absence of significant left valvular regurgitation, only slightly enlarged ventricular volumes.

Doppler measurement may give additional information on cardiac filling characteristics. Commonly made measurements include isovolumic relaxation time, early to atrial left ventricular filling ratio, early left ventricular filling deceleration time, pulmonary venous atrial flow velocity duration and ratio of pulmonary vein systolic and diastolic flow velocities. Age-related changes of these indices have been used. This helps provide evidence of slow left ventricular relaxation or reduced left ventricular diastolic distensibility.

Pulsed Doppler indices of left ventricular filling and pulmonary venous flow are influenced by several physiological variables, such as relaxation, compliance, heart rate, age and filling pressures and may be confounded by suboptimal machine settings and arrhythmias. More recently, colour M-mode recordings of the left ventricular inflow and tissue Doppler diastolic myocardial velocities have been incorporated into the different Doppler filling patterns. All parameters are influenced by increasing age, which adds complexity to the interpretation. In experienced hands, Doppler echocardiography provides haemodynamic measurements, such as cardiac output, stroke volume, pressure gradients, valve area, mitral regurgitant volume and pulmonary artery pressures in the presence of tricuspid and/or pulmonary regurgitation.

Detailed diagnostic criteria for heart failure with diastolic dysfunction (and preserved left ventricular function) have been proposed by the European Study Group on Diastolic Heart Failure<sup>[63]</sup>. However, there is no universally accepted minimal criteria for the diagnosis of diastolic dysfunction. In this context, it is also reasonable to include assessment of left atrial size by volumetric data<sup>[64]</sup>.

When the diagnosis of heart failure has been confirmed by objective evidence of cardiac dysfunction, echocardiography is also helpful in determining its aetiology. Primary valvular lesions can be identified. Regional akinesis or dyskinesis usually implies coronary artery disease, especially in the presence of thin and/or echo-dense myocardium. Echocardiography may document constrictive pericarditis, cardiac amyloidosis or hypertrophic cardiomyopathy.

Transoesophageal echocardiography is not recommended routinely and can only be recommended in patients who have an inadequate echo window, in complicated valvular patients, in those with suspected dysfunction of mechanical mitral valve prosthesis or when it is mandatory to identify or exclude a thrombus in the atrial appendage.

Repeated echocardiography can only be recommended in the follow-up of patients with heart failure when there is an important change in the clinical status suggesting significant improvement or deterioration in cardiac function.

#### *Additional non-invasive tests to be considered*

In patients where echocardiography at rest has not provided enough information and in patients with

coronary artery disease e.g. severe or refractory chronic heart failure and coronary artery disease, further, non-invasive imaging may include:

#### STRESS ECHOCARDIOGRAPHY

Exercise or pharmacological stress echocardiography may be useful for detecting ischaemia as a cause of reversible or persistent dysfunction and in determining the viability of akinetic myocardium<sup>[65]</sup>. Graded dobutamine infusion may be used to recruit contractile reserve<sup>[66]</sup>. Sustained contractile improvement is observed when flow reserve is appropriate, in the presence of stunning or non-transmural infarction. A biphasic response indicates that flow reserve is blunted and suggests the presence of myocardial hibernation. Although several non-controlled studies have shown that revascularization can improve regional function, clinical status and survival in patients with a significant amount of hibernating myocardium<sup>[67,68]</sup>, a systematic assessment of myocardial viability in patients with coronary artery disease and heart failure with systolic dysfunction cannot yet be recommended.

#### NUCLEAR CARDIOLOGY

Radionuclide angiography (RNA) provides reasonably accurate measurements of left, and to a lesser extent, right ventricular ejection fraction and cardiac volumes. Left ventricular filling dynamics can also be analysed. None of these measurements are reliable in the presence of atrial fibrillation. Planar scintigraphy or single photon emission computed tomography (SPECT) can be performed at rest or during stress using infusions of different agents, such as thallium<sup>201</sup> or 99m technetium sestamibi. The presence and extent of ischaemia can be evaluated. Although each of these imaging modalities may have certain diagnostic and prognostic value, the routine use of nuclear cardiology cannot be recommended. As with echocardiography, values of ejection fraction vary with the technique used. Thus, analysis using a single region of interest give values significantly lower than when two regions are used. However, reproducibility is considerably better than echocardiography.

#### CARDIAC MAGNETIC RESONANCE IMAGING (CMR)

CMR is the most accurate and reproducible method for the measurement of cardiac volumes, wall thicknesses and left ventricular mass. It also reliably detects thickened pericardium and quantitates myocardial necrosis, perfusion and function. Quantitative biochemical information, especially on myocardial energetics, can also be obtained by magnetic resonance spectroscopy. This information is presently used as a research tool. At the present time, CMR is only recommended if other imaging techniques have not provided a satisfactory diagnostic answer. However, CMR is a powerful technique and it is too early to define its role in patients with heart failure<sup>[69]</sup>. It is not difficult to imagine that the development of new, and presumably expensive, medicines that have the ability to retard the progression



or even reverse cardiac disease, will necessitate a greater degree of quantitation of cardiac dysfunction than currently is accepted.

#### MODALITY, TECHNIQUE AND OBSERVER VARIABILITY IN MEASUREMENT

Variability within different modalities has been referred to. These are less with RNA and probably least with CMR. Variability between modalities, however, is striking but insufficiently appreciated. In the same individual, values of ejection fraction for example are systematically higher with echo than with RNA and values for CMR seem higher still. This emphasizes the necessity for each institution carrying out non-invasive assessment of ventricular function to know the normal values for the equipment in their hands since the absolute values of ejection fraction will be different for all three modalities.

#### Pulmonary function

- Measurements of lung function are of little value in diagnosing chronic heart failure. However, they are useful in excluding respiratory causes of breathlessness.

Epidemiological studies suggest that there is a strong association between chronic obstructive airways disease and ischaemic heart disease, one of the principal causes of heart failure<sup>[70]</sup>. Forced vital capacity (FVC) is also a valid marker for evaluation of severity (level) and therapy in patients with chronic heart failure<sup>[71]</sup>. FVC and forced expiratory volume (FEV<sub>1</sub>) correlate with maximum oxygen consumption (VO<sub>2</sub> max.) in patients with chronic heart failure. Peak expiratory flow rate (PEFR) and FEV<sub>1</sub> are reduced by chronic heart failure but not to the same extent as in symptomatic obstructive airways disease<sup>[72]</sup>. Other parameters have no value in diagnosing or in grading disease progression in patients with chronic heart failure<sup>[73]</sup>.

Dyspnoea and fatigue are the main causes of exercise limitation in patients with chronic heart failure. Respiratory muscle dysfunction may also play an important role<sup>[74]</sup>.

#### Exercise testing

- In clinical practice exercise testing is of limited value for the diagnosis of heart failure. However, a normal maximal exercise test, in a patient not receiving treatment for heart failure, excludes heart failure as a diagnosis. The main applications of exercise testing in chronic heart failure are more focused on functional and treatment assessment and on prognostic stratification.

Recommendations for exercise testing in heart failure patients have been recently released by the Working Group on Cardiac Rehabilitation & Exercise Physiology and Working Group on Heart Failure of the European Society of Cardiology<sup>[75]</sup>.

Accurate assessment of functional capacity requires that the patient is familiar with what is required. Ideally the test should be individualized and of sufficient duration to achieve target end-points within 8–12 min.

Small increments in workload should be used between stages. The ramp approach (treadmill or bicycle ergometer) appears to facilitate these recommendations for maximal testing. Oxygen uptake is a more stable and reliable measure of exercise tolerance than exercise time. A marked fall in oxygen saturation, PaO<sub>2</sub> and arterio-venous oxygen difference, a reduced ventilatory reserve, a normal oxygen pulse and a normal ratio between VO<sub>2</sub> and workload suggest pulmonary disease.

In recent years, exercise testing has been used for prognostic purposes and exercise capacity is an important component of the risk profile in chronic heart failure. A peak VO<sub>2</sub> <10 ml.kg<sup>-1</sup> min<sup>-1</sup> identifies high risk, and a peak VO<sub>2</sub> >18 ml.kg<sup>-1</sup> min<sup>-1</sup> identifies low risk patients, respectively. Values between these cut-off limits define a 'gray' area of medium risk patients, without further possible stratification by VO<sub>2</sub>. The available prognostic data for women are inadequate. For submaximal testing the 6 min walk test may provide useful prognostic information when walking distance is <300 meters<sup>[76,77]</sup>.

To date there have been no reports of serious problems related to exercise testing in chronic heart failure<sup>[75]</sup>.

#### Invasive investigation

- Invasive investigation is generally not required to establish the presence of chronic heart failure but may be important in elucidating the cause or to obtain prognostic information.

Three diagnostic tools may be helpful in different situations: coronary angiography, haemodynamic monitoring and endomyocardial biopsy. None of them is indicated as a routine procedure.

Cardiac catheterization: Coronary angiography should be considered in patients with acute or acutely decompensated chronic heart failure and in the presence of severe heart failure (shock or acute pulmonary oedema) not responding to initial treatment. Coronary angiography should also be considered in patients with angina pectoris or any other evidence of myocardial ischaemia if not responding to appropriate antiischaemic treatment. Angiography is required to exclude coronary artery disease when a diagnosis of idiopathic dilated cardiomyopathy is considered. Coronary angiography is also indicated in patients with refractory heart failure of unknown aetiology and in patients with evidence of severe mitral regurgitation or aortic valve disease.

Conversely, cardiac catheterization is not recommended in end-stage patients, in patients not considered as candidates for myocardial revascularization or valvular surgery, or in patients with known coronary anatomy in the absence of new episodes of myocardial infarction.

Monitoring of haemodynamic parameters by means of a Swan-Ganz catheter is useful to assess the diagnosis and exclude correctable causes of heart failure. It is also useful in directing treatment of patients with chronic congestive heart failure in the following circumstances: acutely decompensated heart failure not

responding promptly to initial and appropriate treatment; dynamic mitral regurgitation in conjunction with volume overload or exercise, when chronic lung disease is a differential diagnosis and in patients with refractory heart failure not responding to appropriate treatment. Routine right heart catheterization should not be used to tailor chronic therapy.

Endomyocardial biopsy may be useful in selected patients with unexplained (myocardial ischaemia excluded) heart failure. Biopsy may help to differentiate between constrictive and restrictive aetiologies.

#### *Natriuretic peptides*

- Plasma concentrations of certain natriuretic peptides can be helpful in the diagnostic process, especially in untreated patients.

Several clinical and epidemiological studies have related decreasing cardiac, usually left ventricular function with increasing plasma natriuretic peptide concentrations, raising the possibility of a diagnostic 'blood test' for heart failure<sup>[4,29,78]</sup>. Most extensively characterized in this respect are N terminal atrial natriuretic peptide (NT ANP)<sup>[29]</sup>, brain natriuretic peptide (BNP) and its precursor, N terminal pro BNP (NT pro BNP).

Natriuretic peptides have been investigated in heart failure, asymptomatic left ventricular dysfunction and acute myocardial infarction. These peptides may be most useful clinically as a 'rule out' test due to consistent and very high negative prediction values<sup>[3,78,79]</sup>.

Patients suspected of having heart failure, especially in primary care, can be selected for further investigation by echocardiography or other tests of cardiac function on the basis of having an elevated plasma concentration of a natriuretic peptide. In those in whom the concentrations are normal, other causes of dyspnoea and associated symptoms should be considered.

The added value of natriuretic peptides in this situation has yet to be determined. Epidemiological studies suggest that the negative predictive value remains high when individuals at high risk of left ventricular dysfunction are targeted. Future clinical studies will establish the optimal role of natriuretic peptides in the diagnosis of heart failure in screening strategies.

High levels of natriuretic peptides identify those at greatest risk of future serious cardiovascular events including death<sup>[80-82]</sup>. There is also recent evidence that adjusting heart failure therapy in order to reduce natriuretic peptides levels in individual patients may improve outcome<sup>[83]</sup>.

#### *ASSAYS*

Recent developments include user friendly assays of increasing rapidity, suitable for use in 'real time' clinical practice. Time and clinical experience will tell which will be the most successful.

#### *Other neuroendocrine evaluations*

- Other tests of neuroendocrine activation are not recommended for diagnostic or prognostic purposes in individual patients.

Whereas there are no doubts about the importance of neuroendocrine mechanisms in the pathogenesis of heart failure, the role of neuroendocrine factors in the diagnosis is less clear. In large cohorts of patients, there is good evidence that circulating levels of noradrenaline, renin, angiotensin II, aldosterone, endothelin-1 and adrenomedullin are related to the severity and prognosis of heart failure, but in individual patients these predictors are inaccurate and difficult to interpret. Diuretics, vasodilator agents, ACE inhibitors and beta-blockers alter plasma concentrations of neuroendocrine substances in a complex fashion which limits diagnostic use. Plasma noradrenaline rises with age and healthy subjects over the age of 75 years may have plasma concentrations of noradrenaline in the heart failure range<sup>[84]</sup>.

#### *Holter electrocardiography (ambulatory ECG, long time ECG recording-LTER)*

- Conventional Holter monitoring is of no value in the diagnosis of chronic heart failure, though it may detect and quantify the nature, frequency, and duration of atrial and ventricular arrhythmias, which could be causing or exacerbating symptoms of heart failure. Ambulatory electrocardiographic monitoring should be restricted to patients with chronic heart failure and symptomatic arrhythmias.

The high prevalence of ventricular ectopy and ventricular tachycardia is well recognised, but it remains unclear whether ventricular arrhythmias identify patients at high risk of sudden death. In the GESICA trial, patients with non-sustained ventricular tachycardia were found to have significantly more severe heart failure, a higher overall mortality, and a greater incidence of sudden death<sup>[85]</sup>. However, multivariate analysis of CHF-STAT and PROMISE studies support that ventricular arrhythmias are non-specific predictors of mortality. Thus ambulatory electrocardiographic monitoring alone seems not to provide additional prognostic information<sup>[86]</sup>. Furthermore, the finding of asymptomatic complex ventricular arrhythmias on ambulatory electrocardiographic monitoring does not identify specific candidates for antiarrhythmic or device therapy.

#### *HEART RATE VARIABILITY*

Heart rate variability is a marker of autonomic balance and is reduced in heart failure. The diagnostic and prognostic utility of this observation has been extensively investigated<sup>[87-89]</sup>. Correlation between time and frequency domain HRV measures and clinical and haemodynamic variables exists<sup>[90,91]</sup>, and time domain parameters can predict survival independently from clinical and haemodynamic data<sup>[86,92,93]</sup>. Although these data have recently been confirmed in a large, prospective, multicentre study<sup>[87]</sup>. The value of this technology in clinical practice still remains to be determined.

#### *Requirements for the diagnosis of heart failure in clinical practice*

To satisfy the definition of heart failure, symptoms of heart failure and objective evidence of cardiac

**Table 4** Assessments to be performed routinely to establish the presence and likely cause of heart failure

Assessments	The diagnosis of heart failure			Suggests alternative or additional diagnosis
	Necessary for	Supports	Opposes	
Appropriate symptoms	+++		++ (if absent)	
Appropriate signs		+++	+ (If absent)	
Cardiac dysfunction on imaging (usually echocardiography)	+++		+++ (If absent)	
Response of symptoms or signs to therapy		+++	+++ (If absent)	
ECG			+++ (If normal)	
Chest X-ray		If pulmonary congestion or cardiomegaly	+ (If normal)	Pulmonary disease
Full blood count				Anaemia/secondary Polycythaemia
Biochemistry and urinalysis				Renal or hepatic Disease/diabetes
Plasma concentration of natriuretic peptides in untreated patients (where available)	+ (If elevated)	+++ (If normal)		

+ = of some importance; +++ = of great importance.

**Table 5** Additional tests to be considered to support the diagnosis or to suggest alternative diagnosis

Tests	The diagnosis of heart failure		Suggests alternative or additional diagnoses
	Supports	Opposes	
Exercise test	+ (If impaired)	+++ (If normal)	
Pulmonary function tests			Pulmonary disease
Thyroid function tests			Thyroid disease
Invasive investigation and angiography			Coronary artery disease, ischaemia
Cardiac output	+++ (If depressed at rest)	+++ (If normal; especially during exercise)	
Left atrial pressure	+++ (If elevated at rest)	+++ (If normal; in absence of therapy)	

dysfunction must be present (Table 1). The assessment of cardiac function by clinical criteria alone is unsatisfactory. Cardiac dysfunction should be assessed objectively. The echocardiogram is the single most effective tool in widespread clinical use. A diagnosis of heart failure also requires the presence of symptoms and/or signs suggestive of the diagnosis and cannot be made by any single laboratory test. Other conditions may mimic or exacerbate the symptoms and signs of heart failure and need to be excluded (Table 4). An approach to the

diagnosis of heart failure in symptomatic patients is presented in Fig. 2, and should be performed routinely in patients with suspected heart failure in order to establish the diagnosis. Additional tests (Table 5) should be performed or re-evaluated in cases where diagnostic doubt persists or clinical features suggest a reversible cause for heart failure. Coronary artery disease is a common, and probably underdiagnosed, cause of heart failure. If there is reason to believe that the patient will benefit from revascularization then an angiogram should

**Table 6 Management outline**

1. Establish that the patient has heart failure (in accordance with the definition presented on page 1528 diagnosis section)
2. Ascertain presenting features: pulmonary oedema, exertional breathlessness, fatigue, peripheral oedema
3. Assess severity of symptoms
4. Determine aetiology of heart failure
5. Identify precipitating and exacerbating factors
6. Identify concomitant diseases relevant to heart failure and its management
7. Estimate prognosis
8. Anticipate complications
9. Counsel patient and relatives
10. Choose appropriate management
11. Monitor progress and manage accordingly

**Table 7 Aims of treatment**

1. *Prevention*
  - (a) Prevention and/or controlling of diseases leading to cardiac dysfunction and heart failure
  - (b) Prevention of progression to heart failure once cardiac dysfunction is established
2. *Morbidity*  
Maintenance or improvement in quality of life
3. *Mortality*  
Increased duration of life

be done. Figure 2 represents a simplified plan for the evaluation of a patient presenting with symptoms suggestive of heart failure. Table 6 provides a management outline which connects the diagnosis part of the guidelines with the treatment section.

## Treatment of heart failure

### Introduction

Throughout the last decade, the therapeutic approach to heart failure has undergone considerable change. Current treatment not only concerns symptomatic improvement, but focuses increasingly on preventing the transition of asymptomatic cardiac dysfunction to symptomatic heart failure, modulating progression of heart failure and reducing mortality. As this is likely to be a slow process, the effect of novel preventive therapies may only become apparent after a time, in contrast to the often more rapid effects of pure symptomatic treatment. Thus, short- and long-term objectives with individualized therapies should be identified. Important treatment targets include cardiac remodelling, neuro-endocrine and cytokine activation, fluid retention and renal dysfunction. Accordingly, heart failure being a complex syndrome, the therapeutic approach may need several strategies in combination with target different mechanisms.

However, as the therapeutic approaches to heart failure are multiple, including general measures, pharmacological therapy, mechanical devices and surgical interventions, they will not always be applicable in each patient. Adverse effects and interaction between different forms of treatment may preclude their use in some. Rapid deterioration of the clinical condition can require modification of the therapeutic approach.

There are regional differences in the approach to heart failure treatment in Europe. These differences are attributable to variations in aetiology and in health resources. Of more importance, perception and acceptance of the usefulness of and need to prescribe therapies proven to be effective in large controlled trials by the

different physicians taking care of heart failure patients, is slow. Continuous education is clearly needed.

### Aims of treatment in heart failure

The aims of heart failure management are those of the treatment of any disease in general and consist of several components (Table 7).

### Prevention of heart failure

The prevention of heart failure should always be a primary objective. Many potential causes of myocardial damage can be treated and the extent of myocardial damage reduced. Examples include management of risk factors for coronary heart disease, treatment of ischaemia, early triage of acute myocardial infarction, prevention of reinfarction, accurate identification and aggressive treatment of hypertension and some causes of specific heart muscle disease and timely correction of valve disorders and congenital heart disease. However, primary prevention of cardiac dysfunction and heart failure is a large topic, which falls outside the scope of the current Guidelines.

When myocardial dysfunction is already present, the first objective is to remove the underlying cause of ventricular dysfunction if possible (e.g. ischaemia, toxic substances, alcohol, drugs, thyroid disease). The second objective of modern therapy is to modulate progression from asymptomatic left ventricular dysfunction to heart failure. How to modulate progression from asymptomatic left ventricular dysfunction to heart failure is described on page 1550 under Treatment of Asymptomatic Left Ventricular Dysfunction.

### Management of chronic heart failure

The therapeutic approach in chronic heart failure due to systolic cardiac dysfunction consists of general advice and other non-pharmacological measures, pharmacological therapy, mechanical devices and surgery. The currently available types of management are outlined in Table 8.

**Table 8 Treatment options—general advice and measures; exercise and exercise training; pharmacological therapy, devices and surgery**

- Non-pharmacological management
  - General advice and measures
  - Exercise and exercise training
- Pharmacological therapy
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Diuretics
  - Beta-adrenoceptor antagonists
  - Aldosterone receptor antagonists
  - Angiotensin receptor antagonists
  - Cardiac glycosides
  - Vasodilator agents (nitrates/hydralazine)
  - Positive inotropic agents
  - Anticoagulation
  - Antiarrhythmic agents
  - Oxygen
- Devices and surgery
  - Revascularization (catheter interventions and surgery), other forms of surgery
  - Pacemakers
  - Implantable cardioverter defibrillators (ICD)
  - Heart transplantation, ventricular assist devices, artificial heart
  - Ultrafiltration, haemodialysis

The approach to the treatment of specific patient subgroups, i.e. the elderly, or heart failure due to predominant diastolic dysfunction, is addressed in special sections of these guidelines. The treatment of acute heart failure, pulmonary oedema and cardiogenic shock will be presented in a future document.

### Non-pharmacological management

#### General advice and measures

(Level of evidence C for all advice and measures unless stated otherwise.)

#### EDUCATING PATIENTS AND FAMILY

Patients with chronic heart failure and their close relatives should receive general advice (Table 9).

#### WEIGHT CONTROL

Patients are advised to weigh themselves on a regular basis (once a day, twice a week) and, in case of a sudden unexpected weight gain of more than 2 kg in 3 days, to alert a health care provider or adjust their diuretic dose accordingly, e.g. to increase the dose if a sustained increase is noted.

#### DIETARY MEASURES

**Sodium** Controlling the amount of salt in the diet is a problem that is more relevant in advanced heart failure than mild failure. Salt substitutes must be used with caution, as they may contain potassium. In large quantities, in combination with an ACE inhibitor, they may lead to hyperkalaemia<sup>[94]</sup>.

**Table 9 List of subjects to discuss with a heart failure patient and his family**

- General advice
  - Explain what heart failure is and why symptoms occur
  - Causes of heart failure
  - How to recognize symptoms
  - What to do if symptoms occur
  - Self-weighing
  - Rationale of treatments
  - Importance of adhering to pharmacological and non-pharmacological prescriptions
  - Refrain from smoking
  - Prognosis
- Drug counselling
  - Effects
  - Dose and time of administration
  - Side effects and adverse effects
  - Signs of intoxication
  - What to do in case of skipped doses
  - Self-management
- Rest and exercise
  - Rest
  - Work
  - Daily physical activity
  - Sexual activity
  - Rehabilitation
- Vaccinations
- Travel
- Dietary and social habits
  - Control sodium intake when necessary, e.g. some patients with severe heart failure
  - Avoid excessive fluids in severe HF
  - Avoid excessive alcohol intake
  - Stop smoking

**Fluids** Fluid intake must be reduced in patients with advanced heart failure, with or without hyponatremia. The exact amount of fluid restriction remains unclear. In practice, a fluid restriction of 1.5–2 litres is advised in advanced heart failure.

**Alcohol** Moderate alcohol intake is permitted. Alcohol consumption must be prohibited in suspected cases of alcoholic cardiomyopathy. Light-to-moderate alcohol consumption has been reported to improve prognosis in patients with left ventricular dysfunction<sup>[95]</sup>.

#### OBESITY

Treatment of chronic heart failure should include weight reduction in the overweight or obese. The subject is overweight if his/her body mass index (i.e. the actual weight in kilograms divided by height in meters squared) lies between 25 and 30 and obese if it is > 30.

#### ABNORMAL WEIGHT LOSS

Clinical or subclinical malnutrition is present in about 50% of patients with severe chronic heart failure<sup>[4]</sup>. The wasting of total body fat and lean body mass that accompanies weight loss is called cardiac cachexia<sup>[96]</sup>. Cardiac cachexia is an important predictor of reduced survival<sup>[97]</sup>.

Consider the possibility of abnormal weight loss when

- (a) a body weight <90% of ideal body weight or,
- (b) a documented non-intentional weight loss of at least 5 kg or of more than 7.5% of the previous normal non-oedematous weight in the previous 6 months and/or a body mass index (weight/height<sup>2</sup>) less than 22 kg . m<sup>-2</sup>.

The aim of treatment is to achieve an increase in non-oedematous body weight, preferably by increasing muscle mass through adequate physical exercise. Small, frequent meals are indicated when reduced food intake results from nausea, dyspnoea or a bloated feeling.

#### SMOKING

Smoking should always be discouraged. The use of smoking cessation aids should be actively encouraged, and may include nicotine replacement therapies.

#### TRAVELLING

High altitudes or very hot or humid places should be discouraged. In general, short air flights are preferable to long journeys by other means of transport. In patients with severe heart failure, long air flights can cause problems (e.g. dehydration, excessive limb oedema, deep venous thrombosis) and patients should be cautioned. It is also worth discussing potential effects of changes in diet on gastrointestinal equilibrium during journeys. The use of diuretics and vasodilators may have to be adapted in cases of excessive sodium and fluid loss in hot humid climates.

#### SEXUAL ACTIVITY

It is not possible to dictate guidelines about sexual activity counselling. Recommendations are given to reassure the not severely compromised, but frightened patient, to reassure the partner who is often even more frightened, and perhaps refer the couple for specialist counselling. Advise, if appropriate, the use of sublingual nitrates before sex and discourage major emotional involvements. Patients in NYHA class II are at intermediate risk and class III-IV are at high risk of cardiac decompensation triggered by sexual activity<sup>[98]</sup>.

#### ADVICE ON IMMUNIZATIONS

There is no documented evidence of the effects of immunization in patients with heart failure. Pneumococcal and influenza immunization may reduce the incidence of respiratory infections that may worsen heart failure.

#### DRUG COUNSELLING

Self-management (when practical) of the dose of the diuretic, based on changes in symptoms and fluid balance should be encouraged. Within pre-specified and individualized limits patients are able to adjust their diuretics.

Desired effects and side effects of all drugs should be explained. In addition, the following information on drugs should be provided: improvement may be gradual and only complete after several weeks, and with some drugs, months of treatment; the need for gradual titration with ACE inhibitors and beta-blocking drugs to desired dosage levels which will not directly improve the patient's symptoms; in case dehydration occurs (diarrhoea, profuse sweating in hot climates) to reduce the dose of diuretics; how to act if symptomatic hypotension occurs (reduction of the diuretic and, if necessary, temporary reduction of the ACE inhibitor dose); that coughing might occur with the use of ACE inhibitors as well as a decrease in taste; to avoid non-steroidal inflammatory agents in combination with ACE inhibitors; possible use of nitrates, in sublingual or spray form, as a transitory symptomatic treatment, administered at the onset of acute dyspnoea, or as prevention in certain situations.

#### DRUGS TO AVOID OR BEWARE

The following drugs should be used with caution when co-prescribed with any form of heart failure treatment, or avoided<sup>[99]</sup> (for example see relevant pages):

- (1) Non-steroidal antiinflammatory drugs (NSAIDs)
- (2) Class I antiarrhythmics (page 1548)
- (3) Calcium antagonists (verapamil, diltiazem, first generation dihydropyridine derivatives (page 1547)
- (4) Tricyclic antidepressants
- (5) Corticosteroids
- (6) Lithium

#### *Rest, exercise and exercise training*

##### REST

Rest should not be encouraged in stable chronic heart failure. When there is acute heart failure or destabilization of chronic heart failure, physical rest or bed-rest is necessary. Passive mobilization exercises are carried out in order to prevent untoward effects resulting from prolonged bed-rest and attenuate the risk of venous thrombosis. As the clinical condition of the patient improves, respiratory exercises and active mobilization can be carried out.

##### EXERCISE

If in a stable condition, the patient should be encouraged to carry out daily physical and leisure time activities that do not induce symptoms, to prevent muscle de-conditioning. Strenuous or isometric exercises and competitive and tiring sport should be discouraged. If the patient is employed, the work tasks carried out must be assessed and advice given on whether they can be continued.

##### EXERCISE TRAINING

Exercise training programmes are encouraged in stable patients in NYHA class II-III. In clinical practice, exercise intolerance in chronic heart failure has a multifactorial aetiology. Changes in the periphery rather than

Table 10 Exercise training

**Steady state training**

**Frequency of sessions** Short multiple daily sessions of 5–10 min should be advised to more compromised patients. longer (20–30 min) sessions 3–5 times a week should be recommended to patients with good functional capacity.

**Intensity of training sessions** Initial improvements of aerobic capacity and symptoms in traditional programmes occur at 4 weeks. The maximum time required to attain peak responses in physical and cardiopulmonary variables is 16 and 26 weeks, respectively; then responses plateau. Three stages of progression have been observed: an initial stage, improvement, and maintenance stage.

Initial stage: intensity should be kept at a low level (e.g. 40–50% peak  $\text{VO}_2$ ), increasing the exercise duration from 5 to 15 min. Exercise duration and frequency of training is increased according to symptoms and clinical status.

During the improvement stage, the gradual increase of intensity (50%, 60%, 70% and even 80%, if tolerated, of peak  $\text{VO}_2$ ) is the primary aim; prolongation of a session to 15–20 min, and if tolerated up to 30 min, is a secondary goal.

The maintenance stage in exercise programmes usually begins after the first 6 months of training. Further improvements may be minimal, but continuing the exercise training is important. Effects of a 3-week residential training programme were lost after only 3 weeks of activity restriction, suggesting the need for implementing long-term exercise training into the therapy management of chronic heart failure.

**Interval training**

**Cycling** With cycling, work phases of 30 s and recovery phases of 60 s may be useful with an intensity of 50% of maximum short term exercise capacity, determined with the patient starting with unloaded pedalling for 3 min and then increasing the work rate by 25 Watts every 10 s. During the recovery phase, patients pedal at 10 Watts.

**Treadmill** On a treadmill, work and recovery phases of 60 s each may be used.

left ventricular performance itself are important determinants of exercise capacity. Several small clinical and mechanistic studies and some randomized trials showed that regular exercise can safely increase physical capacity by 15–25%, improve symptoms and perception of quality of life in patients with stable class II and III heart failure (level of evidence B). No significant deleterious effects or significant deterioration in central haemodynamics have been reported with exercise training.

Standardized recommendations for exercise training in heart failure patients by the European Society of Cardiology have recently been published<sup>[100]</sup>.

The exercise training can be performed by either interval or steady state exercise, applying intensities of 60–80% of the predetermined peak heart rate. Interval training methods may allow for more intense exercise stimuli on peripheral muscles than obtained during steady state training, but without inducing greater cardiovascular stress. Exercise training should be performed in the following order: duration, then frequency, then intensity. Details are provided in Table 10.

### Pharmacological therapy

#### Angiotensin-converting enzyme inhibitors

- ACE inhibitors are recommended as first-line therapy in patients with a reduced left ventricular systolic function expressed as a subnormal ejection fraction, i.e. <40–45% (see non-invasive imaging page 1532) (level of evidence A).
- ACE inhibitors should be uptitrated to the dosages shown to be effective in the large, controlled trials in

heart failure (level A), and not titrated based on symptomatic improvement alone (level C).

#### ACE INHIBITORS IN ASYMPTOMATIC LEFT VENTRICULAR DYSFUNCTION

Asymptomatic patients with a documented left ventricular systolic dysfunction benefit from long-term ACE inhibitor therapy. The consistency of data from the SOLVD Prevention Study, SAVE and TRACE have shown that asymptomatic patients, but with left ventricular dysfunction, will have less development of symptomatic heart failure and hospitalizations for heart failure<sup>[12,101]</sup> (level of evidence A).

#### ACE INHIBITORS IN SYMPTOMATIC HEART FAILURE

All patients with symptomatic heart failure due to systolic left ventricular dysfunction should receive an ACE inhibitor (level of evidence A).

ACE inhibition significantly improves survival and symptoms and reduces hospitalization in patients with moderate and severe heart failure and left ventricular systolic dysfunction. In the absence of fluid retention, ACE inhibitors should be given first. In patients with fluid retention together with diuretics (level of evidence B).

A recent meta-analysis in 12 763 patients with left ventricular dysfunction and/or heart failure from five large controlled trials, including three that included patients early after myocardial infarction, showed that ACE inhibition significantly reduces mortality, admissions for heart failure and reinfarction, independent of age, sex, and baseline use of diuretics, aspirin and beta-blockade. Benefit was apparent over the full range of left ventricular function at baseline<sup>[11,102]</sup>.

**Table 11 Doses of ACE inhibitors shown to be effective in large, controlled trials of heart failure or left ventricular dysfunction**

	Studies of mortality		
	Drug	Target dose	Mean daily dose
<i>Studies in chronic heart failure</i>			
Consensus Trial Study Group, 1978 <sup>[192]</sup>	Enalapril	20 mg b.i.d.	18.4 mg
Cohn <i>et al.</i> (V-HeFT II, 1991) <sup>[142]</sup>	Enalapril	10 mg b.i.d.	15.0 mg
The SOLVD Investigators, 1991 <sup>[193]</sup>	Enalapril	10 mg b.i.d.	16.6 mg
ATLAS <sup>[109]</sup>	Lisinopril	High dose:	32.5–35 mg daily
		Low dose:	2.5–5 mg daily
<i>Studies after MI LV dysfunction with or without HF</i>			
Pfeffer <i>et al.</i> (SAVE, 1992) <sup>[194]</sup>	Captopril	50 mg t.i.d.	(not available)
AIRE <sup>[103]</sup>	Ramipril	5 m b.i.d.	(not available)
TRACE <sup>[101]</sup>	Trandolapril	4 mg daily	(not available)

LV=left ventricular; MI=myocardial infarction; HF=heart failure.

The absolute benefit is greatest in patients with most severe heart failure. ACE inhibition markedly enhances survival in patients with signs or symptoms of heart failure during the acute phase of myocardial infarction, even if the symptoms are transient<sup>[103]</sup>. In addition to these effects of mortality, ACE inhibitors in general improve the functional status of patients with heart failure. In contrast, only small benefits in exercise capacity occur. Moreover, whereas ACE inhibitors may prevent further deterioration of left ventricular function and attenuate further cardiac dilatation, they do not consistently reduce cardiac size<sup>[104,105]</sup>. Also, beneficial effects on cardiac function may quickly diminish in magnitude upon cessation of ACE inhibition<sup>[104,106]</sup>.

ACE inhibitors should always be uptitrated to the target dose used in large controlled clinical trials, if tolerated, to reduce long-term morbidity and mortality. ACE inhibitors should not be titrated based on symptomatic improvement.

Important adverse effects associated with ACE inhibitors are hypotension, syncope, renal insufficiency, hyperkalaemia and angioedema. Although cough may often be due to heart failure or concomitant diseases, e.g. respiratory disease, dry cough is a side effect of ACE inhibitors. Severe cough may lead to discontinuation of ACE inhibitor therapy. Some patients may tolerate reinstitution of the ACE inhibitor after a drug-free period. Substitutes for ACE inhibitors in this situation include angiotensin receptor antagonists or, if contraindicated, the combination of high-dose nitrate and hydralazine. Observational data would argue against using an NSAID to suppress cough, as heart failure may deteriorate. Sodium cromoglycate or thromboxane synthetase inhibition may suppress cough during ACE inhibitor treatment<sup>[107]</sup>.

Changes in systolic and diastolic blood pressure and increases in serum creatinine are usually small in normotensive patients. Moderate renal insufficiency and a relatively low blood pressure (serum creatinine up to 250  $\mu\text{mol} \cdot \text{l}^{-1}$  and systolic blood pressure as low as 90 mmHg) are no contraindications to ACE inhibitor

treatment. Serum creatinine might increase by 10–15% in patients with severe heart failure, irrespective of baseline serum creatinine<sup>[108]</sup>. In most of these patients creatinine levels will either remain stable or decrease towards pre-treatment values during continued treatment. It should be stressed that mortality is higher among patients with elevated creatinine levels and that these patients in particular benefit from treatment with ACE inhibitors. The risk of hypotension and renal dysfunction increases in patients with severe heart failure, those treated with high doses of diuretics, elderly patients and patients with renal dysfunction or hyponatraemia. In addition, changes in serum potassium are usually small (0.2 mmol  $\cdot \text{l}^{-1}$ ). Mild hyperkalaemia is no contraindication to use ACE inhibitors. However, serum potassium levels  $>5.5 \text{ mmol} \cdot \text{l}^{-1}$  are a contraindication. If potassium-sparing diuretics were prescribed to correct serum potassium levels they should be stopped during initiation of ACE inhibitor therapy.

Absolute contraindications for initiation of ACE inhibitor treatment are bilateral renal artery stenosis and angioedema during previous ACE inhibitor therapy.

The effect of ACE inhibition in heart failure has been documented in target doses that are usually higher than those used in clinical practice. Furthermore, in the ATLAS trial morbidity expressed as hospitalizations for heart failure, was less in patients with a higher than a lower dose regimen<sup>[109]</sup>. Target maintenance dose ranges of ACE inhibitors shown to be effective in various trials are shown in Table 11.

Recommended initiating and maintenance dosages of ACE inhibitors which have been approved for the treatment of heart failure in Europe are presented in Table 12. The dose of ACE inhibitor should always be initiated at the lower dose level and titrated to the target dose. The recommended procedures for starting an ACE inhibitor are given in Table 13.

#### INITIATING ACE INHIBITOR THERAPY (TABLE 13)

Until further trials are completed, the dose of the chosen ACE inhibitor should be titrated up to the maximum



**Table 12 Recommended ACE inhibitor maintenance dose-ranges\***

Drug	Initiating dose	Maintenance dose
Benazepril	2.5 mg	5–10 mg b.i.d.
Captopril	6.25 mg t.i.d.	25–50 mg t.i.d.
Enalapril	2.5 mg daily	10 mg b.i.d.
Lisinopril	2.5 mg daily	5–20 mg daily
Quinapril	2.5–5 mg daily	5–10 mg daily
Perindopril	2 mg daily	4 mg daily
Ramipril	1.25–2.5 mg daily	2.5–5 mg b.i.d.
Cilazapril	0.5 mg daily	1–2.5 mg daily
Fosinopril	10 mg daily	20 mg daily
Trandolapril	1 mg daily	4 mg daily

\*Manufacturers' or regulatory recommendations.

target dose used in clinical trials. Careful attention should be given to the locally approved prescribing information when initiating therapy.

Regular monitoring of renal function is recommended: (1) before, 1–2 weeks after each dose increment, at 3 months, and at 6 monthly intervals; (2) when treatment is changed, which may affect renal function; (3) in patients with past or present renal dysfunction or electrolyte disturbances, more frequent measurements should be made.

Care should be taken in patients with a low systolic blood pressure or a serum creatinine above  $250 \mu\text{mol} \cdot \text{l}^{-1}$ . Patients with a systolic level below 100 mmHg should have therapy initiated under specialist medical care. Low blood pressures ( $<90 \text{ mmHg}$ ) during ACE inhibitor treatment are acceptable if the patient is asymptomatic.

#### Diuretics

##### LOOP DIURETICS, THIAZIDES AND METOLAZONE

- Diuretics are essential for symptomatic treatment when fluid overload is present and manifest as

pulmonary congestion or peripheral oedema (level of evidence A), although there are no controlled, randomized trials that have assessed the effect on survival of these agents. The use of diuretics results in rapid improvement of dyspnoea and increased exercise tolerance (level of evidence B)<sup>[110,111]</sup>.

- Diuretics should always be administered in combination with ACE inhibitors if possible (level of evidence C).

Detailed recommendations and major side effects are outlined in Tables 14 and 15.

Loop diuretics, thiazides and metolazone are all used at various stages in the treatment of heart failure. Mild heart failure can be treated with a thiazide diuretic, but as heart failure worsens a loop diuretic is usually necessary. At equivalent doses, all loop diuretics produce a comparable increase in urine output. Patients with severe heart failure often require increasing doses of loop diuretics. This may be due to worsening renal function or decreased gastrointestinal absorption of furosemide. Intravenous drug administration, and in particular continuous intravenous infusion, often overcomes the diuretic resistance<sup>[112]</sup>.

Thiazide diuretics are less effective if the glomerular filtration rate falls below  $30 \text{ ml} \cdot \text{min}^{-1}$ , a situation that is commonly encountered in elderly patients with heart failure. In severe heart failure thiazides have a synergistic effect with loop diuretics and may be used in combination<sup>[113]</sup>. It is probable that this combination is superior in terms of efficacy or adverse effects to increasing the dose of a loop diuretic. Metolazone is a powerful diuretic, which is often used as a drug of last resort added to loop diuretics, but is not available in all European countries.

##### Potassium-sparing diuretics

- Potassium-sparing diuretics should only be prescribed if hypokalaemia persists despite ACE

**Table 13 The recommended procedure for starting an ACE inhibitor**

1. Review the need for and dose of diuretics and vasodilators
2. Avoid excessive diuresis before treatment. Reduce or withhold diuretics, if being used, for 24 h.
3. It may be advisable to start treatment in the evening, when supine, to minimize the potential negative effect on blood pressure, although there are no data on heart failure to support this (evidence C). When initiated in the morning, supervision for several hours with blood pressure control is advisable.
4. Start with a low dose (Table 12) and build up to maintenance dosages shown to be effective in large trials (Table 11).
5. If renal function deteriorates substantially, stop treatment.
6. Avoid potassium-sparing diuretics during initiation of therapy.
7. Avoid non-steroidal antiinflammatory drugs (NSAIDs).
8. Check blood pressure, renal function and electrolytes 1–2 weeks after each dose increment, at 3 months and subsequently at 6 monthly intervals.

The following patients should be referred for specialist care:

1. Cause of heart failure unknown
2. Systolic blood pressure  $<100 \text{ mmHg}$
3. Serum creatinine  $>150 \mu\text{mol} \cdot \text{l}^{-1}$
4. Serum sodium  $<135 \text{ mmol} \cdot \text{l}^{-1}$
5. Severe heart failure
6. Valve disease as primary cause

**Table 14 Diuretics****Initial diuretic treatment**

- Loop diuretics or thiazides.  
Always administered in addition to an ACE inhibitor.
- If GFR  $< 30 \text{ ml} \cdot \text{min}^{-1}$  do not use thiazides, except as therapy prescribed synergistically with loop diuretics.

**Insufficient response:**

1. increase dose of diuretic
2. combine loop diuretics and thiazides
3. with persistent fluid retention: administer loop diuretics twice daily
4. in severe chronic heart failure add metolazone with frequent measurement of creatinine and electrolytes.

**Potassium-sparing diuretics: triamterene, amiloride, spironolactone**

- Use only if hypokalaemia persists after initiation of therapy with ACE inhibitors and diuretics.
- Start 1-week low-dose administration, check serum potassium and creatinine after 5–7 days and titrate accordingly. Recheck every 5–7 days until potassium values are stable.

GFR=glomerular filtration rate; CHF=chronic heart failure; ACE=angiotensin converting-enzyme.

**Table 15 Diuretics (oral): dosages and side effects**

	Initial dose (mg)		Maximum recommended daily dose (mg)		Major side effects
<b>Loop diuretics</b>					
Furosemide	20–40		250–500		Hypokalaemia, hypomagnesaemia, hyponatraemia
Bumetanide	0.5–1.0		5–10		Hyperuricaemia, glucose intolerance,
Torsemide	5–10		100–200		Acid-base disturbance
<b>Thiazides</b>					
Hydrochlorothiazide	25		50–75		Hypokalaemia, hypomagnesaemia, hyponatraemia
Metolazone	2.5		10		Hyperuricaemia, glucose intolerance,
Indapamide	2.5		2.5		Acid-base disturbance
<b>Potassium-sparing diuretic</b>	<b>+ACEI</b>	<b>–ACEI</b>	<b>+ACE</b>	<b>–ACEI</b>	
Amiloride	2.5	5	20	40	Hyperkalaemia, rash
Triamterene	25	50	100	200	Hyperkalaemia
Spironolactone	25	50	50	100–200	Hyperkalaemia, gynaecomastia

inhibition or, in severe heart failure despite the combination ACE inhibition and low-dose spironolactone (level of evidence C).

- Potassium supplements are less effective in this situation (level of evidence B).

Most patients on diuretics for heart failure will also be treated with an ACE inhibitor. Until recently the combination of potassium sparing diuretics and ACE inhibitors was regarded as potentially dangerous. One small, controlled study suggested that the administration of spironolactone at dosages that result in diuresis and natriuresis, i.e. 50–100 mg, to patients who are not responding to loop diuretics and ACE inhibition, may result in rapid weight reduction without hyperkalaemia<sup>[114]</sup>. However, at present potassium-sparing diuretics such as triamterene, amiloride and relatively high dosages of spironolactone should only be considered if there is persisting diuretic-induced hypokalaemia despite concomitant ACE inhibitor therapy, or in severe heart failure, despite concomitant ACE inhibition plus low-dose spironolactone (level of evidence C). Similar restrictions also pertain in cases of intolerance to

ACE inhibition and replacement therapy with angiotensin receptor blockers. Oral potassium supplements are less effective in maintaining body potassium stores during diuretic treatment<sup>[115]</sup>. In general, the use of all potassium sparing diuretics should be monitored by repeated measurements of serum creatinine and potassium. A practical approach is to measure serum creatinine and potassium every 5–7 days after initiation of treatment until the values are stable. Thereafter, measurements can be made every 3–6 months.

**Beta-adrenoceptor antagonists**

- Beta-blocking agents are recommended for the treatment of all patients with stable, mild, moderate and severe heart failure from ischaemic or non-ischaemic cardiomyopathies and reduced left ventricular ejection fraction, in NYHA class II to IV, on standard treatment, including diuretics and ACE inhibitors, unless there is a contraindication (level of evidence A).
- In patients with left ventricular systolic dysfunction, with or without symptomatic heart failure, following

**Table 16** *The recommended procedure for starting a beta-blocker*

1. Patients should be on a background therapy with ACE inhibition, if not contraindicated.
2. The patient should be in a relatively stable condition, without the need of intravenous inotropic therapy and without signs of marked fluid retention.
3. Start with a very low dose (Table 17) and titrate up to maintenance dosages shown to be effective in large trials. The dose may be doubled every 1–2 weeks if the preceding dose was well tolerated. Most patients can be managed as out-patients.
4. Transient worsening failure, hypotension or bradycardia may occur during the titration period or thereafter
  - Monitor the patient for evidence of heart failure symptoms, fluid retention, hypotension and bradycardia
  - If worsening of symptoms, first increase the dose of diuretics or ACE-inhibitor; temporarily reduce the dose of beta-blockers if necessary
  - If hypotension, first reduce the dose of vasodilators; reduce the dose of the beta-blocker if necessary
  - Reduce or discontinue drugs that may lower heart rate in the presence of bradycardia; reduce dose of beta-blockers if necessary, but discontinue only if clearly necessary.
  - Always consider the reintroduction and/or up-titration of the beta-blocker when the patient becomes stable.
5. If inotropic support is needed to treat a decompensated patient on beta-blockade, phosphodiesterase inhibitors should be preferred because their haemodynamic effects are not antagonized by beta-blocker agents.

*The following patients should be referred for specialist care:*

- Severe heart failure Class III/IV
- Unknown aetiology
- Relative contraindications: bradycardia, low blood pressure
- Intolerance to low doses
- Previous use of beta-blocker and discontinuation because of symptoms
- Suspected asthma or bronchial disease

*Contraindications to beta-blockers in patients with heart failure*

- Asthma bronchiale
- Severe bronchial disease
- Symptomatic bradycardia or hypotension

an acute myocardial infarction long-term beta-blockade is recommended in addition to ACE inhibition to reduce mortality (level of evidence B).

The first recommendation is based on data obtained from large and small studies including over 15 000 patients<sup>[116–127]</sup>, the second on the recently published CAPRICORN study with carvedilol<sup>[195]</sup>. In several large, randomized, placebo-controlled mortality trials carvedilol<sup>[121,124,196]</sup>, bisoprolol<sup>[125]</sup> and metoprolol<sup>[126,127]</sup> have been associated with a long-term reduction in total mortality, cardiovascular mortality, sudden death and death due to progression of heart failure in patients in functional class II–IV. In these studies, beta-blocking therapy also reduces hospitalizations (all, cardiovascular and heart failure), improves the functional class and leads to less worsening of heart failure than placebo. This beneficial effect has been consistently observed in subgroups of different age, gender, functional class, left ventricular ejection fraction and ischaemic or non-ischaemic aetiology (level of evidence A).

Although a reduction in mortality and hospitalization has been demonstrated with several beta-blockers in chronic heart failure, a class-effect has not been established. In one large trial, no benefit on survival was observed with bucindolol (BEST)<sup>[128]</sup>. Accordingly, only bisoprolol, carvedilol and metoprolol can be recom-

mended at present. A direct comparison of different beta-blockers is currently being evaluated in the COMET trial (metoprolol vs carvedilol). In smaller, controlled studies beta-blockade has been shown to improve ventricular function<sup>[120,129,130]</sup>. In contrast, exercise capacity usually does not improve.

Further data are needed to establish the effects of beta-blocking agents in certain demographic groups, such as elderly subjects (>75 years), certain racial subsets and atrial fibrillation. In SENIORS the effect of beta-blockade (nebivolol) in the elderly patient with heart failure is investigated.

#### INITIATION OF THERAPY

As beta-blocker action may be biphasic with long-term improvement, possibly preceded by initial worsening, beta-blockers should be initiated under careful control. The initial dose should be small and increased slowly and progressively to the target dose used in the large clinical trials. Up-titration should be adapted to individual response. Beta-blockers may reduce heart rate excessively, may temporarily induce myocardial depression and precipitate heart failure. In addition, beta-blockers may initiate or exacerbate asthma and induce peripheral vasoconstriction. Table 16 gives the recommended procedure for the use of beta-blockers in clinical practice and contraindications. Table 17 shows the

**Table 17** Initiating dose, target dose and titration scheme of beta-blocking agents as used in recent large, controlled trials

Beta-blocker	First dose (mg)	Increments (mg . day <sup>-1</sup> )	Target dose (mg . day <sup>-1</sup> )	Titration period
Bisoprolol <sup>[125]</sup>	1.25	2.5, 3.75, 5, 7.5, 10	10	weeks—month
Metoprolol tartrate <sup>[119]</sup>	5	10, 15, 30, 50, 75, 100	150	weeks—month
Metoprolol succinate CR <sup>[126]</sup>	12.5/25	25, 50, 100, 200	200	weeks—month
Carvedilol <sup>[121, 196]</sup>	3–125	6.25, 12.5, 25, 50	50	weeks—month

Daily frequency of administration as in the trials referenced above.

titration scheme of the drugs used in the most relevant studies.

#### Aldosterone receptor antagonists — spironolactone

- Aldosterone antagonism is recommended in advanced heart failure (NYHA III–IV), in addition to ACE inhibition and diuretics to improve survival and morbidity (level of evidence B).

Although spironolactone was developed as a diuretic agent at a higher dose level, it is now understood that aldosterone has an important role in the pathophysiology of heart failure. It promotes vascular and myocardial fibrosis, potassium and magnesium depletion, sympathetic activation, parasympathetic inhibition and baroreceptor dysfunction<sup>[131, 132]</sup>. ACE inhibitors insufficiently suppress circulating aldosterone levels<sup>[133]</sup>.

The RALES mortality trial showed that low dose spironolactone (12.5–50 mg) on top of an ACE inhibitor and a loop diuretic markedly and progressively improved survival of patients in advanced (NYHA class III or IV) heart failure, irrespective of aetiology<sup>[134]</sup>. At this dose, spironolactone is believed not to have an appreciable diuretic effect. Both death from progressive heart failure and sudden cardiac death were reduced in RALES and although only 11% received a beta-blocker, the mortality reduction was significant in this pre-specified subgroup. Whether an aldosterone antagonist could be useful in patients with class II heart failure or asymptomatic left ventricular dysfunction remains to be established.

Administration and dosing considerations are provided in Table 18.

#### ADVERSE EFFECTS OF SPIRONOLACTONE

If painful gynecomastia develops (10% in RALES), spironolactone may need to be stopped. The new selective aldosterone receptor antagonist eplerenone, with a lower affinity for androgen and progesterone receptors than spironolactone, may reduce the risk of gynecomastia, but needs further evaluation. Ongoing trials will assess the effect of eplerenone on morbidity and mortality.

#### Angiotensin II receptor antagonists

- Angiotensin II receptor antagonists (ARBs) could be considered in patients who do not tolerate ACE

**Table 18** Administration and dosing considerations with spironolactone

- 1 Consider whether a patient is in severe heart failure (NYHA III–IV) despite ACE inhibition/diuretics
- 2 Check serum potassium (<5.0 mmol . l<sup>-1</sup>) and creatinine (<250 µmol . l<sup>-1</sup>)
- 3 Add 25 mg spironolactone daily
- 4 Check serum potassium and creatinine after 4–6 days
- 5 If at any time serum potassium >5.5 mmol . l<sup>-1</sup>, reduce dose by 50%. Stop if serum potassium >5.5 mmol . l<sup>-1</sup>.
- 6 If after 1 month symptoms persevere and normokalaemia exists, increase to 50 mg daily. Check serum potassium/creatinine after 1 week.

inhibitors for symptomatic treatment (level of evidence C).

- However, it is unclear whether ARBs are as effective as ACE inhibitors for mortality reduction (level of evidence B).
- In combination with ACE inhibition, ARBs may improve heart failure symptoms and reduce hospitalizations for worsening heart failure (level of evidence B).

#### SAFETY AND TOLERABILITY

Side effects, notably cough are significantly less than with ACE inhibitors<sup>[135]</sup>. In the majority of studies, mainly carried out in hypertension, the side effect profile of ARBs is comparable to placebo. The ELITE study, comparing the safety and tolerability of losartan with that of captopril in elderly patients with heart failure, found no difference in the incidence of renal dysfunction between the two drugs after 1 year's follow-up<sup>[136]</sup>. Monitoring of renal function is as essential with ARBs as with ACE-inhibitors. ARBs studied or under investigation in heart failure are given in Table 19.

#### COMPARATIVE STUDIES OF ARBs AND ACE INHIBITORS IN HEART FAILURE

Thus far, ARBs have not been shown to be superior to ACE inhibitors, although side effects may be less with the ARB<sup>[137]</sup>. In Elite II a possible negative interaction of losartan and beta-blocker therapy was observed. Further studies are ongoing.

#### COMBINING ACE INHIBITORS AND ARBs IN HEART FAILURE

Angiotensin II can be produced from non-ACE pathways, and during angiotensin II receptor blockade

**Table 19** Currently available angiotensin II receptor antagonists

Drug	Daily dose (mg)
Losartan	50–100
Valsartan	80–320
Irbesartan	150–300
Candesartan cilexetil	4–16
Telmisartan	40–80
Eprosartan	400–800

levels of angiotensin II rise, thus competing with the antagonist. This has led to the hypothesis that the combination of an ACE inhibitor and an ARB may be beneficial. In VAL-HeFT, patients were randomized to placebo or valsartan on top of standard therapy, which included an ACE inhibitor in nearly all. The results showed no difference in overall mortality, but a reduction in the combined end-point all-cause mortality or morbidity expressed as hospitalization because of worsening heart failure<sup>[138]</sup>. In patients who also received a beta-blocker a trend towards a negative effect of the ARB was observed. Whether a possible interaction truly exists needs to be clarified in further studies. In the ongoing CHARM-add on study, patients with heart failure and left ventricular dysfunction are randomized to placebo or candesartan cilexetil on top of an ACE inhibitor.

#### Cardiac glycosides

- Cardiac glycosides are indicated in atrial fibrillation and any degree of symptomatic heart failure, whether or not left ventricular dysfunction is the cause, in order to slow ventricular rate, thereby improving ventricular function and symptoms (level of evidence B)<sup>[139]</sup>.
- A combination of digoxin and beta-blockade appears superior than either agent alone (level of evidence C)<sup>[140]</sup>.

In sinus rhythm, digoxin is recommended to improve the clinical status of patients with persisting heart failure symptoms due to left ventricular systolic dysfunction despite ACE inhibitor and diuretic treatment (level of evidence B). Insufficient data are available for patients with heart failure due to left ventricular systolic dysfunction and sinus rhythm on the combined treatment of ACE inhibition, beta-blockade, diuretics and, in severe heart failure, spironolactone.

Digoxin and digitoxin are the most frequently used cardiac glycosides. They have identical pharmacodynamic effects, but different pharmacokinetic profiles. Elimination of digoxin is renal. In contrast, digitoxin is metabolised in the liver and is less dependent on renal function, potentially useful in renal dysfunction and in elderly patients.

In the DIG trial in 6800 patients with an ischaemic and non-ischaemic cardiomyopathy and mild-to-moderate heart failure, long-term digoxin did not

improve survival and a small decrease in the risk of death-from-heart failure was offset by an increase in the risk of death from other causes<sup>[141]</sup>. Thus, the primary benefit and indication for digoxin in heart failure is to reduce symptoms and improve clinical status, and thereby to decrease the risk of hospitalization for heart failure without an impact on survival.

Contraindications to the use of cardiac glycosides include bradycardia, second- and third-degree AV block, sick sinus syndrome, carotid sinus syndrome, Wolff-Parkinson-White syndrome, hypertrophic obstructive cardiomyopathy, hypokalaemia, and hypercalcaemia.

#### DIGOXIN

The usual daily dose of oral digoxin is 0.25–0.375 mg if serum creatinine is in the normal range (in the elderly 0.625–0.125 mg, occasionally 0.25 mg). No loading dose is needed when treating chronic conditions. The treatment can be initiated with 0.25 mg bid. for 2 days. Renal function and plasma potassium should always be measured before starting treatment. In renal failure, the daily doses should be reduced accordingly. As the digoxin clearance closely approximates to creatinine clearance, the latter should be measured or calculated by the Cockcroft and Gault formula, which is provided in Table 3.

#### Vasodilator agents in chronic heart failure

- There is no specific role for vasodilators in the treatment of heart failure (level A), although they may be used as adjunctive therapy for angina or concomitant hypertension (level of evidence C).
- In case of intolerance to ACE inhibitors ARBs are preferred to the combination hydralazine–nitrates (level of evidence A).

#### HYDRALAZINE-ISOSORBIDE DINITRATE

Vasodilator agents may be used as adjunctive therapy in the management of heart failure. In previous guidelines, the hydralazine-isosorbide dinitrate combination was suggested as an alternative when ACE inhibitors are contraindicated or cannot be tolerated<sup>[2, 142]</sup>. Recent data would suggest that angiotensin-II type-1 antagonists are the preferred medication in that situation (level of evidence B, see page 1545).

Relatively high doses of hydralazine (up to 300 mg) in combination with high-dose isosorbide dinitrate (up to 160 mg) without ACE inhibition may have some beneficial effect on mortality, but not on hospitalization for heart failure<sup>[143]</sup>. At these doses, the combination increased exercise performance more than with enalapril. There is no evidence of proven benefit when either nitrates or hydralazine are used alone in addition to current therapy.

Nitrates may be used for the treatment of concomitant angina or relief of acute dyspnoea. Early development of haemodynamic tolerance (tachyphylaxis) to nitrates may occur with frequent dosing (every

4–6 h), but is less with intervals of 8 to 12 h<sup>[144]</sup> or in conjunction with ACE-inhibitors or hydralazine<sup>[145]</sup>.

#### ALPHA-ADRENERGIC BLOCKING DRUGS

There is no evidence to support the use of alpha-adrenergic blocking drugs in heart failure (level of evidence B).

#### CALCIUM ANTAGONISTS

In general, calcium antagonists are not recommended for the treatment of heart failure due to systolic dysfunction. Diltiazem and verapamil-type calcium antagonists in particular are not recommended in heart failure due to systolic dysfunction, and are contraindicated in addition to beta-blockade (level of evidence C).

Newer calcium antagonists (felodipine, amlodipine) in addition to baseline therapy including ACE inhibitors and diuretics do not provide a better effect on survival compared to placebo<sup>[146,147]</sup> (level of evidence A).

As long-term safety data with felodipine and amlodipine indicate a neutral effect on survival, they may be considered as additional therapy for concomitant arterial hypertension or angina.

#### Positive inotropic therapy

- Inotropic agents are commonly used to limit severe episodes of heart failure or as a bridge to heart transplantation in end-stage heart failure (level of evidence C). However, treatment-related complications may occur and their effect on prognosis is not well recognized.
- Repeated or prolonged treatment with oral inotropic agents increases mortality (level of evidence A).
- Currently, insufficient data are available to recommend dopaminergic agents for heart failure treatment.

#### POSITIVE INOTROPIC AGENTS

Intravenous inotropic therapy is used to correct the haemodynamic disturbances of severe episodes of worsening heart failure. The agent most often used in this setting is dobutamine. However, its use has been insufficiently documented in controlled trials and the effects of dobutamine on prognosis are not well characterized. Problems related to use of dobutamine are tachyphylaxis, increase in heart rate and often an inadequate vasodilatory effect. Similar problems are present with other cAMP-dependent inotropes, i.e. phosphodiesterase inhibitors such as amrinone, milrinone or enoximone.

In acute heart failure, intravenous milrinone does not reduce the number of hospitalizations or cardiovascular events, but leads to a higher incidence of treatment-related complications, such as atrial fibrillation and hypotension as compared to placebo<sup>[147]</sup>. In studies with oral treatment, milrinone, enoximone, vesnarinone and amrinone invariably increase arrhythmias and mortality.

For acute worsening of heart failure, the short-term administration of levosimendan, a new inotrope with calcium-sensitising properties, appears to be safer than dobutamine<sup>[148]</sup>. Also, in acute heart failure after

myocardial infarction, levosimendan improved symptoms and halved mortality during the first 72 h, a difference in mortality which was maintained over the next 6 months<sup>[149]</sup>. However, this effect on mortality requires further confirmation in formal trials.

#### DOPAMINERGIC AGENTS

Currently, there are insufficient data available to recommend oral dopamine analogues for the treatment of heart failure. The dopaminergic agent ibopamine, which also has sympathomimetic properties, is not recommended for the treatment of chronic heart failure due to systolic left ventricular dysfunction (level of evidence B)<sup>[150]</sup>.

Intravenous dopamine is used for the short-term correction of haemodynamic disturbances of severe episodes of worsening heart failure. At low dosages ( $3\text{--}5\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ ) it may improve renal blood flow. Its use has not been evaluated in prospective controlled trials and its effects on prognosis are not well defined.

#### Antithrombotic agents

- There is little evidence to show that antithrombotic therapy modifies the risk of death, or vascular events in patients with heart failure other than in the setting of atrial fibrillation when anticoagulation is firmly indicated (level of evidence C)<sup>[151]</sup>, and prior myocardial infarction when either aspirin or oral anticoagulants should be used as secondary prophylaxis.

Patients with heart failure are at high risk of thrombo-embolic events. Ischaemic heart disease is the commonest cause of heart failure and coronary vascular occlusion is the commonest vascular event in this population. However, patients with heart failure are also at greatly increased risk of stroke and other vascular events<sup>[152]</sup>. Many cases of sudden death may be precipitated primarily by vascular, rather than arrhythmic events<sup>[153]</sup>.

The reported annual risk of stroke in controlled heart failure studies is between 1 and 2%, and the risk of myocardial infarction from 2 to 5.4%, respectively. The annual risk of stroke in the Stroke Prevention of Atrial Fibrillation study (SPAF) was 10.3% in atrial fibrillation patients with definite heart failure and 17.7% in those with recent heart failure<sup>[154]</sup>.

Oral anticoagulants reduce the risk of stroke in heart failure patients with atrial fibrillation<sup>[155]</sup>. However, there is a lack of evidence to support the use of antithrombotic therapy in patients in sinus rhythm, even if they have had a previous vascular event or evidence of intra-cardiac thrombus. There is little evidence to suggest that patients with layered left ventricular thrombus are at increased risk of thrombo-embolic events. There is evidence that patients with mobile intra-cardiac thrombi are at increased risk of thrombo-embolic events, but no conclusive evidence to show that surgery or antithrombotic therapy reduces this risk.

The little evidence that exists from randomized controlled trials of anti-thrombotic therapy in heart failure

has failed to show a conclusive difference between antithrombotic therapy and none, or between different antithrombotic therapies. There is controversy over a possible adverse interaction between aspirin and ACE inhibitors<sup>[102,156]</sup>. In summary, in the absence of conclusive evidence, it would be inappropriate to make any recommendations about chronic antiplatelet or anticoagulant therapy for patients with heart failure in sinus rhythm.

Many patients with acute decompensation of heart failure require admission to hospital and bed rest. Randomized controlled trials which have included such patients suggest that low molecular weight heparins may reduce the risk of deep venous thrombosis, at least when used in higher doses<sup>[157]</sup>. The studies conducted so far have failed to show that this reduces the risk of pulmonary embolism although trends to reduced mortality (a possible presentation of pulmonary embolism) were observed. Evidence to support the use of unfractionated heparins and comparative studies between heparins are lacking. Low molecular weight heparins should be used prophylactically in patients on bed-rest with severe heart failure (level of evidence C).

#### Antiarrhythmics

- In general, there is no indication for the use of antiarrhythmic agents in heart failure (level of evidence C).

Indications for antiarrhythmic drug therapy in the individual patient include atrial fibrillation (rarely flutter), non-sustained or sustained ventricular tachycardia.

#### CLASS I ANTIARRHYTHMICS

Class I antiarrhythmics should be avoided as they have pro-arrhythmic effects on the ventricular level and an adverse effect on haemodynamics and prognosis in heart failure (level of evidence C).

#### CLASS II ANTIARRHYTHMICS

Beta-blockers reduce sudden death in heart failure (level of evidence A) (see also page 1544). They may also be indicated alone or in combination with amiodarone or non-pharmacological therapy in the management of sustained or non-sustained ventricular tachyarrhythmias. (Level of evidence C)<sup>[158]</sup>.

#### CLASS III ANTI-ARRHYTHMICS

Amiodarone is effective against most supraventricular and ventricular arrhythmias (level of evidence B). It may restore and maintain sinus rhythm in patients with heart failure and atrial fibrillation even in the presence of enlarged left atria, or improve the success of electrical cardioversion and is the preferred treatment in this condition<sup>[159]</sup>. Amiodarone is the only antiarrhythmic drug without clinically relevant negative inotropic effects.

Large trials have shown that prophylactic use of amiodarone in patients with non-sustained, asymptomatic ventricular arrhythmias and heart failure does not

affect total mortality<sup>[160]</sup>. The risk of adverse effects, such as hyper- and hypothyroidism, hepatitis, pulmonary fibrosis and neuropathy, although shown to be relatively low in recent, large, placebo-controlled trials must be weighed against the potential benefits of amiodarone. Lower doses (100–200 mg day<sup>-1</sup>) may reduce the risk. Routine administration of amiodarone in patients with heart failure is not justified (level of evidence B). Dofetilide, a new class III agent, was found to be safe in heart failure patients as no modification of total mortality was noted<sup>[161]</sup> (level of evidence B).

### Oxygen therapy

Oxygen is used for the treatment of acute heart failure, but at present has no application in chronic heart failure. Oxygen supplementation may lead to haemodynamic deterioration in severe heart failure<sup>[162]</sup>. In patients with cor pulmonale, long-term oxygen therapy has been shown to reduce mortality<sup>[163]</sup>.

### Devices and surgery

*Revascularization procedures, mitral valve surgery, cardiomyoplasty and partial left ventriculotomy*

- Surgical treatment should be directed towards the underlying aetiology and mechanisms. In addition to revascularization, it is important to approach patients with significant valvular disease, e.g. aortic stenosis, before they develop significant left ventricular dysfunction.

#### REVASCULARIZATION

There are no controlled data to support the use of revascularization procedures for the relief of heart failure symptoms, but in the individual patient with heart failure of ischaemic origin revascularization may lead to symptomatic improvement (level of evidence C).

Revascularization of patients with heart failure of ischaemic origin is performed with increasing success since chronic left ventricular dysfunction does not necessarily mean permanent or irreversible cell damage. Chronically hypoperfused or repetitively stunned myocytes may remain viable but be hypo- or akinetic. This type of dysfunction is called 'hibernating myocardium'<sup>[164]</sup>. However, demonstration of viability or contractile reserve is essential for a good outcome<sup>[165]</sup>.

Nevertheless, there remains a strong negative correlation of operative mortality and left ventricular ejection fraction, as outlined in the analysis of the Society of Thoracic Surgeons database ([WWW.CTSNET.ORG/doc1727](http://WWW.CTSNET.ORG/doc1727)). Here, a low left ventricular ejection fraction (<25%) was associated with increased operative mortality. Also, advanced heart failure symptoms (NYHA IV) resulted in a greater mortality rate than in patients with mild to moderate heart failure.

A study comparing the effect of symptomatic heart failure and left ventricular dysfunction independently,

showed a stronger correlation of NYHA class with operative mortality than left ventricular ejection fraction<sup>[166]</sup> preferred in heart failure patients with bradyarrhythmias whenever possible.

Off pump coronary revascularization may lower the surgical risk for heart failure patients undergoing surgical revascularization<sup>[167]</sup>. Controlled studies on this future subject are pending.

#### MITRAL VALVE SURGERY

Mitral valve surgery in patients with severe left ventricular dysfunction and severe mitral valve insufficiency may lead to symptomatic improvement in selected heart failure patients (level of evidence C).

This is also true for secondary mitral insufficiency due to left ventricular dilatation. Several observational studies have indicated excellent early and intermediate term outcome of mitral reconstruction in patients with end-stage cardiomyopathy<sup>[168,169]</sup>.

#### CARDIOMYOPLASTY

Currently, cardiomyoplasty cannot be recommended for the treatment of heart failure (level of evidence C).

Cardiomyoplasty has only been applied in a very limited number of patients and is still undergoing investigation. Class IV patients should be avoided since they have a high operative mortality. Cardiomyoplasty cannot be considered a viable alternative to heart transplantation (level of evidence C).

#### PARTIAL LEFT VENTRICULOTOMY (BATISTA OPERATION)

Currently, partial left ventriculotomy cannot be recommended for the treatment of heart failure (level of evidence C).

Partial, lateral resection of the left ventricle plus or minus mitral valve surgery initially gained interest for treatment of end stage heart failure patients. However, in recent studies a number of patients required ventricular assist devices or subsequent transplantation for failed surgery<sup>[170]</sup>. The Batista operation cannot be considered an alternative to heart transplantation<sup>[171]</sup> (level of evidence C).

#### Pacemakers

- Pacemakers have no established role in the treatment of heart failure except for conventional bradycardia indication.
- Resynchronization therapy using bi-ventricular pacing may improve symptoms and sub-maximal exercise capacity (level of evidence B), but its effect on mortality and morbidity is as yet unknown.

#### CONVENTIONAL INDICATION

Pacemakers have had no established role in the treatment of heart failure except for conventional bradycardia indication.

In retrospective studies, lower morbidity and prolonged survival by AV synchronous pacing has been reported in patients with chronic high degree AV block or sinus node disease and concomitant heart failure<sup>[172,173]</sup>. Therefore, AV synchronous pacing should be

#### RESYNCHRONIZATION THERAPY

During resynchronization therapy with biventricular pacing, both ventricles are stimulated nearly simultaneously. It is estimated that 30% of patients with severe heart failure have intraventricular conduction disturbances resulting in discoordinated ventricular contraction<sup>[174]</sup>. This electromechanical disturbance could be partially overcome by biventricular pacing resulting in a more coordinated ventricular contraction<sup>[174-177]</sup>.

Acute and short-term haemodynamic benefits of left ventricular or biventricular pacing include decreases in filling pressures and mitral regurgitation and improvements in diastolic filling and cardiac output<sup>[175,177]</sup>. It remains to be determined whether these benefits translate into long term improvements.

Several small randomized controlled studies of permanent biventricular pacing indicate a substantial improvement of symptoms and submaximal exercise capacity. Whether biventricular pacing favourably influences morbidity and mortality will be answered by several recently initiated controlled studies.

#### Arrhythmia devices and surgery

##### IMPLANTABLE CARDIOVERTER DEFIBRILLATORS (ICD)

- There is as yet no specifically defined role for ICD in chronic heart failure (level of evidence C). A available data from controlled trials have not specifically addressed the effect of ICD in heart failure patients.

In patients with documented sustained ventricular tachycardia or ventricular fibrillation, the ICD is highly effective in treating recurrences of these arrhythmias either by antitachycardia pacing or cardioversion-defibrillation, thereby reducing morbidity and the need for rehospitalization.

ICD therapy improves survival in patients who have survived cardiac arrest, or who have sustained ventricular tachycardia which is either poorly tolerated or associated with reduced systolic left ventricular function (level of evidence A).

ICD have proven to be beneficial in patients at high risk of sudden death i.e. with a history of myocardial infarction and reduced systolic left ventricular function<sup>[177-179]</sup>. Although all these trials included a significant percentage of patients with a history of heart failure, they did not address specifically the role of ICD in heart failure patients.

Several ongoing trials have now included patients with both left ventricular systolic dysfunction and heart failure.

#### RADIOFREQUENCY CATHETER ABLATION

Catheter ablation may be indicated in patients with heart failure and reciprocating tachycardias or selected patients with atrial fibrillation. However, there is insufficient data on the role of ablation on sustained



**Table 20** Contraindications for heart transplantation

- Present alcohol and/or drug abuse
- Lack of proper cooperation
- Chronic mental disease, which could not be properly controlled
- Treated cancer with remission and <5 years follow-up
- Systemic disease with multiorgan involvement
- Uncontrolled infection
- Severe renal failure (creatinine clearance  $<50 \text{ ml. min}^{-1}$ ) or creatinine  $>250 \mu\text{mol. l}^{-1}$ , although some centers accept patients on haemodialysis
- Fixed high pulmonary vascular resistance (6–8 Wood units and mean transpulmonary gradient  $>15 \text{ mmHg}$  and pulmonary artery systolic pressure  $>60 \text{ mmHg}$ )
- Recent thromboembolic complication
- Unhealed peptic ulcer
- Evidence of significant liver impairment
- Other disease with a poor prognosis

ventricular tachycardias in patients with heart failure. It may be an adjunctive therapy to implantable cardioverter defibrillators in some patients.

#### *Heart transplantation, ventricular assist devices and artificial heart*

##### HEART TRANSPLANTATION

- Heart transplantation is an accepted mode of treatment for end-stage heart failure. Although controlled trials have never been conducted, it is considered to significantly increase survival, exercise capacity, return to work and quality of life compared to conventional treatment, provided proper selection criteria are applied (level of evidence C).

Recent results in patients on triple immunosuppressive therapy have shown a 5-year survival of approximately 70–80%<sup>[180]</sup> and return to full-time or part-time work, or seeking employment after 1 year in about 2/3 of the patients in the best series<sup>[181]</sup>.

Combined treatment with ACE inhibitors and beta-blockers has markedly improved outcome and quality of life for patients with severe heart failure to the extent that a significant number of patients are now being withdrawn from the transplant waiting list.

Patients who should be considered for heart transplantation are those with severe heart failure with no alternative form of treatment. Predictors of poor survival are taken into account. The patient must be willing and capable to undergo intensive medical treatment, and be emotionally stable so as to withstand the many uncertainties likely to occur both before and after transplantation. The contraindications for heart transplantation are shown in Table 20. Besides shortage of donor hearts, the main problem of heart transplantation is rejection of the allograft, which is responsible for a considerable percentage of deaths in the first post-operative year. The long-term outcome is limited predominantly by the consequences of immuno-suppression (infection, hypertension, renal failure, malignancy, and by transplant coronary vascular disease.

##### VENTRICULAR ASSIST DEVICES AND ARTIFICIAL HEART

Current indications for ventricular assist devices and artificial heart include bridging to transplantation,

transient myocarditis and in some permanent haemodynamic support (level of evidence C).

At present, biventricular support is only possible with external blood pumps. This approach is of limited duration due to infectious complications and is therefore used for short-term bridging (months) until cardiac transplantation.

Left ventricular assist devices are being implanted in increasing numbers of heart failure patients. As the majority of these would fulfil criteria for heart transplantation, the methodology is used as a bridge for transplantation. However, due to the scarcity of donor organs, there are many patients now with duration of support of more than 1 year. Indications for patients beyond those fulfilling the criteria for heart transplantation may be possible in the future. Complications are mainly of infectious or thrombo-embolic nature and would currently limit broader application of this technology as long-term implants. Fully implantable devices are now being tested in clinical trials.

##### Ultrafiltration

Ultrafiltration has been used for patients with pulmonary oedema and/or severe refractory congestive heart failure. Ultrafiltration can resolve pulmonary oedema and overhydration in case of refractoriness to pharmacological therapies<sup>[182]</sup>. In most patients with severe disease the relief is temporary<sup>[183]</sup>.

#### *Choice and timing of pharmacological therapy*

The choice of pharmacological therapy in the various stages of heart failure due to systolic dysfunction is displayed in Tables 21a and 21b. Before initiating therapy, the correct diagnosis needs to be established and considerations should be given to the Management Outline presented in Table 6.

##### *Asymptomatic systolic left ventricular dysfunction*

In general, the lower the ejection fraction, the higher the risk of developing heart failure. Treatment with an ACE inhibitor is recommended in patients with reduced

Table 21a Chronic heart failure — choice of pharmacological therapy

LV systolic dysfunction	ACE inhibitor	Diuretic	Beta-blocker	Aldosterone antagonists
Asymptomatic LV dysfunction	Indicated	Not indicated	Post MI	Not indicated
Symptomatic HF (NYHA II)	Indicated	Indicated if fluid retention	Indicated	Not indicated
Worsening HF (NYHA III-IV)	Indicated	Indicated, combination of diuretics	Indicated (under specialist care)	Indicated
End-stage HF (NYHA IV)	Indicated	Indicated, combination of diuretics	Indicated (under specialist care)	Indicated

HF=heart failure; LV=left ventricular; MI=myocardial infarction.

Table 21b Chronic heart failure — choice of pharmacological therapy

LV systolic dysfunction	Angiotensin II receptor antagonists	Cardiac glycosides	Vasodilator (hydralazine/isosorbide dinitrate)	Potassium-sparing diuretic
Asymptomatic LV dysfunction	Not indicated	With atrial fibrillation	Not indicated	Not indicated
Symptomatic HF (NYHA II)	If ACE inhibitors are not tolerated and not on beta-blockade	(a) when atrial fibrillation (b) when improved from more severe HF in sinus rhythm Indicated	If ACE inhibitors and angiotensin II antagonists are not tolerated	If persisting hypokalaemia
Worsening HF (NYHA III/IV)	If ACE inhibitors are not tolerated and not on beta-blockade		If ACE inhibitors and angiotensin II antagonists are not tolerated	If persisting hypokalaemia
End-stage HF (NYHA IV)	If ACE inhibitors are not tolerated and not on beta-blockade	Indicated	If ACE inhibitors and angiotensin II antagonists are not tolerated	If persisting hypokalaemia

HF=heart failure; LV=left ventricular.

systolic function as indicated by a substantial reduction in left ventricular ejection fraction (see section on imaging in the Diagnosis section) (recommendation page 1540). In patients with asymptomatic left ventricular dysfunction following an acute myocardial infarction add a beta-blocker (recommendation page 1543).

*Symptomatic systolic left ventricular dysfunction — heart failure NYHA Class II (Figure 3)*

Without signs of fluid retention: ACE inhibitor (recommendation page 1540). Titrate to the target dose used in large controlled trials (Table 11). Add a beta-blocker (recommendation page 1543) and titrate to target dosages used in large controlled trials (Table 17).

If patients remain symptomatic:

Consider alternative diagnosis.

When ischaemia is suspected, consider nitrates or revascularization before adding a diuretic.

Consider the potential benefit of other surgical procedures, i.e. aneurysmectomy, valve surgery, when applicable.

Add a diuretic.

With signs of fluid retention: Diuretics in combination with an ACE inhibitor and a beta-blocker.

First, the ACE inhibitor and diuretic should be co-administered. When symptomatic improvement occurs, i.e. fluid retention disappears, try to reduce the dose of diuretic, but the optimal dose of the ACE inhibitor should be maintained. To avoid hyperkalaemia, any potassium-sparing diuretic should be omitted from the diuretic regimen before introducing an ACE inhibitor. Potassium-sparing diuretics may be added if hypokalaemia persists. Add a beta-blocker and titrate to target dosages used in large controlled trials (Table 17). Patients in sinus rhythm receiving cardiac glycosides, who have improved from severe to mild heart failure, should continue cardiac glycoside therapy (page 1546). In case of intolerance to ACE inhibition or beta-blockade, consider addition of an ARB to the remaining drug (recommendation page 1545). Avoid adding an ARB to the combination ACE inhibitor and a beta-blocker (page 1546).

*Worsening heart failure (Fig. 3)*

The most frequent causes of worsening heart failure are shown in Table 22. Patients in NYHA class III who have improved from NYHA class IV during the preceding 6 months or are currently NYHA class IV should receive low-dose spironolactone (12.5–50 mg daily, recommendation page 1545). Cardiac glycosides are often added.

	For symptoms	For survival/morbidity <i>Mandatory therapy</i>	For symptoms if intolerance to ACE inhibitor or beta- blockade
NYHA I	Reduce/stop diuretic	Continue ACE inhibitor if asymptomatic. Add beta-blocker if post MI	
NYHA II	+/- diuretic depending on fluid retention	ACE inhibitor as first-line treatment ↓ Add beta-blocker if still symptomatic	ARB if ACE inhibitor intolerant  or ACE inhibitor + ARB if beta-blocker intolerant
NYHA III	+ diuretics + digitalis if still symptomatic + nitrates/hydralazine if tolerated	ACE inhibitor and beta-blockade add spironolactone,  ↓	ARB if ACE inhibitor intolerant  or ACE inhibitor + ARB if beta-blocker intolerant
NYHA IV	Diuretics + digitalis + nitrates/hydralazine if tolerated + temporary inotropic support	ACE inhibitor beta-blockade spironolactone	ARB if ACE inhibitor intolerant  or ACE inhibitor + ARB if beta-blocker intolerant

**Figure 3** Pharmacological therapy of symptomatic chronic heart failure due to systolic left ventricular dysfunction.

Loop diuretics can be increased in dose. Combinations of diuretics (a loop diuretic with a thiazide) are often helpful. Consider heart transplantation or reconsider any benefit that might be derived from coronary revascularization procedures, aneurysmectomy or valve surgery.

*End-stage heart failure (patients who persist in NYHA IV despite optimal treatment and proper diagnosis (Fig. 3)*

Patients should be (re)considered for heart transplantation. In addition to the pharmacological treatments

outlined in the above sections, intermittent inotropic support (intravenous sympathomimetic agents, dopaminergic agonists and/or phosphodiesterase agents) can be used in end-stage heart failure, but always should be considered as an interim approach to further treatment that will benefit the patient.

For patients on the waiting list for transplantation bridging procedures, circulatory support with intra-aortic balloon pumping or ventricular assist devices, haemofiltration or dialysis may sometimes be necessary. These should be used only in the context of a strategic plan for the long-term management of the patient.

Palliative treatment in terminal patients should always be considered and may include the use of opiates for the relief of symptoms.

**Table 22** Most frequent causes of worsening heart failure

*Non-cardiac*

- Non-compliance to the prescribed regimen (salt, liquid, medication)
- Recently co-prescribed drugs (antiarrhythmics other than amiodarone, beta-blockers, non-steroidal anti-inflammatory drugs, verapamil, diltiazem)
- Alcohol abuse
- Renal dysfunction (excessive use of diuretics)
- Infection
- Pulmonary embolism
- Thyroid dysfunction (e.g. amiodarone)
- Anaemia (hidden bleeding)

*Cardiac*

- Atrial fibrillation
- Other supraventricular or ventricular arrhythmias
- Bradycardia
- Appearance or worsening of mitral or tricuspid regurgitation
- Myocardial ischaemia (frequently symptomless), including myocardial infarction
- Excessive preload reduction (diuretics + ACE inhibitors)

*Management of heart failure due to diastolic dysfunction*

There is still little evidence from clinical trials or observational studies as to how to treat diastolic dysfunction. Also there is much debate about the prevalence of heart failure due to pure diastolic dysfunction. Although recent epidemiological studies suggest that in the elderly the percentage of patients hospitalized with heart failure-like symptoms and a normal systolic left ventricular function may be as high as 35–45%, there is uncertainty about the prevalence of diastolic dysfunction in patients with heart failure symptoms and a normal systolic function in the community.

Heart failure with preserved left ventricular systolic function and that due to diastolic dysfunction are not synonymous. The former diagnosis implies the evidence of preserved left ventricular ejection fraction and not the demonstration of left ventricular diastolic dysfunction. The diagnosis of pure diastolic heart failure also requires

evidence of abnormal diastolic function, which may be difficult to assess in atrial fibrillation.

Causes of diastolic heart failure include: myocardial ischaemia, hypertension, myocardial hypertrophy and myocardial/pericardial constriction. These should be identified and treated appropriately. Precipitating factors should be identified and corrected, in particular tachy-arrhythmias should be prevented and sinus rhythm restored whenever possible.

#### PHARMACOTHERAPY OF DIASTOLIC HEART FAILURE

The recommendations provided below are largely speculative, as limited data exist in patients with preserved left ventricular systolic function or diastolic dysfunction (level of evidence C), patients being excluded from nearly all large controlled trials in heart failure.

- (1) Beta-blockade to lower heart rate and increase the diastolic period.
- (2) Verapamil-type calcium antagonists may be used for the same reason. Some studies with verapamil have shown a functional improvement in patients with hypertrophic cardiomyopathy<sup>[184]</sup>.
- (3) ACE inhibitors may improve relaxation and cardiac distensibility directly, may have a long-term effect through regression of hypertrophy and reduce hypertension.
- (4) Diuretics may be necessary when episodes with fluid overload are present, but should be used cautiously so as not to lower preload excessively and thereby reduce stroke volume and cardiac output.

In general, the treatment of this condition remains difficult and often unsatisfactory. One of the main problems here is that pure diastolic dysfunction may be rare, the condition often occurring in conjunction with some degree of systolic dysfunction. As conditions under which diastolic dysfunction occurs vary between patients and no controlled data from studies exist, straightforward therapeutic algorithms are not easy to provide for the individual.

#### Heart failure treatment in the elderly

Heart failure occurs predominantly among elderly patients with a median age of about 75 years in community studies. Because ageing is frequently associated with multi-morbidity, an important proportion of the heart failure population is likely to have one or several co-morbid conditions. Frequent concomitant diseases are renal failure, obstructive lung disease, diabetes, stroke and anaemia. Such patients also receive multiple drugs, which includes the risk of unwanted interactions and may reduce compliance.

The therapeutic approach to systolic dysfunction in the elderly should be principally identical to that in younger heart failure patients with respect to the choice of drug treatment. Due to altered pharmacokinetic and pharmacodynamic properties of cardiovascular drugs in the elderly, therapy should be applied more cautiously. Sometimes reduced dosages are necessary. Renal dysfunction is of special importance since some cardio-

vascular drugs that are used frequently, such as most ACE inhibitors and digoxin, are excreted in active form in the urine (for calculating the creatinine clearance see Table 3, Diagnosis section). Other complicating factors include diastolic dysfunction, blunting of receptor function and orthostatic dysregulation of the blood pressure.

A sedentary lifestyle with deconditioning and reduced skeletal mass, and changes in nutritional habits leading to reduced caloric/protein intake are further complicating factors in the management of the elderly heart failure patient.

#### ACE inhibitors

ACE inhibitors are effective and well tolerated by the elderly patients in general. Due to a greater likelihood for hypotension and delayed excretion rate of most ACE inhibitors low dose titration is advisable. Initiation of ACE inhibitor therapy should be supervised if possible with monitoring of supine and standing blood pressure, renal function and serum potassium levels. With such precautions treatment can be introduced in the outpatient setting.

#### Diuretic therapy

In the elderly, thiazides are often ineffective due to reduced glomerular filtration. Reduced absorption rate and bio-availability of drugs or increased excretion rate of thiazides or loop diuretics may lead to delayed onset, prolonged duration or sometimes reduced drug action. On the other hand diuretics often cause orthostatic hypotension and/or further reduction in renal function.

Potassium sparing diuretics, such as amiloride and triamterene, exhibit delayed elimination. In elderly patients, hyperkalaemia is more frequently seen with a combination of potassium sparing diuretics and ACE inhibitors or NSAIDs.

#### Beta-blockers

Beta-blocking agents are surprisingly well tolerated in the elderly if patients with contraindications such as sick sinus node, AV-block and obstructive lung disease are excluded.

Currently used beta-blockers in heart failure are eliminated by hepatic metabolism and do not require dosage reduction in patients with decreased renal function. Initiation of beta-blockade should, however, be carried out with low dosages and prolonged periods of titration. Beta-blockade should not be withheld because of increasing age alone.

#### Cardiac glycosides

Elderly patients may be more susceptible to adverse effects of digoxin. This glycoside is mainly eliminated in active form by the kidney and therefore half-lives increase up to two- to three fold in patients aged over 70 years. Initially, low dosages are recommended in patients with elevated serum creatinine.

#### Vasodilator agents

Venodilating drugs, such as nitrates, hydralazine and the combination of these drugs should be administered

carefully due to the risk of hypotension. Little data exist concerning the efficacy and safety of vasodilating drugs in the treatment of elder heart failure patients.

#### Arrhythmias

- In the approach to arrhythmia it is essential to recognise and correct precipitating factors, improve cardiac function and reduce neuro-endocrine activation with beta-blockade, ACE inhibition and possibly aldosterone receptor antagonists (level of evidence C).

Both supraventricular and ventricular arrhythmias occur frequently in heart failure. Sudden death accounts for approximately 40–50% of all deaths, decreasing in relative proportion in advancing stages of heart failure. Various mechanisms, i.e. structural cardiac changes, myocardial ischaemia and neurohormonal activation may play a role. Further precipitating factors for arrhythmias include electrolyte disturbances (hypokalaemia, hypomagnesaemia and hyperkalaemia), drug interaction with cardiac pump function or electrical stability, such as some calcium antagonists and some antiarrhythmic agents, digitalis toxicity and intercurrent diseases, e.g. hyperthyroidism and respiratory diseases.

#### Ventricular arrhythmias

- In patients with ventricular arrhythmias, the use of antiarrhythmic agents is only justified in patients with severe, symptomatic, sustained ventricular tachycardias and amiodarone should be the preferred agent (level of evidence B)<sup>[85,160]</sup>.

The routine use of antiarrhythmic agents for asymptomatic premature ventricular complexes or non-sustained ventricular tachycardias is not justified (see section on Antiarrhythmics page 1548). The indications of ICD therapy in patients with heart failure are restricted to patients with life threatening ventricular arrhythmias i.e. ventricular fibrillation or sustained ventricular tachycardia and in selected post-infarction patients at high risk of sudden death (level of evidence A)<sup>[177–179]</sup>.

Electrophysiological studies may be indicated in selected, high risk patients with left ventricular dysfunction and coronary artery disease with non-sustained ventricular tachycardia (level of evidence B).

#### Atrial fibrillation

For persistent (non self-terminating) atrial fibrillation, electrical cardioversion should always be considered, although its success rate may depend on the duration of atrial fibrillation and left atrial size. However, there is no evidence in patients with persistent atrial fibrillation and heart failure, suggesting that restoring and maintaining sinus rhythm is superior to control of heart rate. Amiodarone may convert atrial fibrillation to sinus rhythm and improve the success rate of electrical cardioversion.

In patients with atrial fibrillation and heart failure or/and depressed left ventricular function the use of antiarrhythmic therapy to maintain sinus rhythm should

**Table 23 Recommended components of programs (level of evidence C)**

- use a team approach
- vigilant follow-up, first follow-up within 10 days of discharge
- discharge planning
- increased access to health care
- optimizing medical therapy with guidelines
- intense education and counselling
  - inpatient and outpatient (home-based)
  - attention to behavioural strategies
  - address barriers to compliance
- early attention to signs and symptoms
- flexible diuretic regimen

be restricted to amiodarone (level of evidence C) and, if available, to dofetilide (level of evidence B)<sup>[161]</sup>. Anticoagulation in chronic atrial fibrillation with warfarin should always be considered unless contraindicated in patients with persistent atrial fibrillation and chronic heart failure (level of evidence C).

In permanent (cardioversion not attempted or failed) atrial fibrillation, rate control is mandatory. In asymptomatic patients, beta-blockade, digitalis glycosides or the combination may be considered. In symptomatic patients digitalis glycosides are the first choice (level of evidence C). If digoxin or warfarin are used in combination with amiodarone, their dosages may need to be adapted.

#### Symptomatic systolic left ventricular dysfunction and concomitant angina or hypertension

Specific recommendations in addition to general treatment for heart failure due to systolic left ventricular dysfunction.

If angina is present:

1. optimize existing therapy, e.g. beta-blockade.
2. consider coronary revascularization.
3. add long-acting nitrates.
4. if not successful: add second generation dihydropyridine derivatives.

If hypertension is present:

1. optimize dose ACE inhibitors, beta-blocking agents and diuretics.
2. add spironolactone or ARBs if not present already.
3. if not successful: try second generation dihydropyridine derivatives.

#### Care and follow-up (Table 23)

Comprehensive non-pharmacological intervention programmes are helpful in improving quality of life, reducing readmission and decreasing cost (level of evidence B). However, it is unclear how best to organize

the content of these programmes. Different models (e.g. heart failure outpatient clinic, heart failure nurse specialist, community nurse specialist, patient tele-monitoring) may be appropriate depending on the stage of the disease, patient population and national resources (level of evidence C).

Readmission of heart failure patients relates to medical factors (e.g. uncontrolled hypertension, infections), environmental factors (e.g. failing social support), behavioural factors (e.g. non-compliance with drugs, diet or other life-style modifications) or to factors related to discharge planning (e.g. early discharge, inadequate patient education)<sup>[185]</sup>.

Various management programmes, aiming at optimizing individual care of heart failure patients, have been evaluated; these are mainly non-pharmacological and only some are controlled. Most programmes were reported to be effective in improving quality of life, reducing the number of readmissions and in reducing costs<sup>[186,187]</sup>. Only a few studies have reported limited or negative outcomes<sup>[188-190]</sup>.

Although basic agreement can be achieved on the content of care needed by patients with heart failure (for example all patients should be properly counselled, see pages 1538 and 1539), the organization of the care should be closely adapted to the needs of the patient group and the resources of the organization.

Depending on the health care system of each country, it seems important to determine which health care provider is the most appropriate to participate in various components. Nurses can play an important role in these innovative forms of care.

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## Appendix 1

### Task Force

(if not stated otherwise representing WG on Heart Failure):

Co-chairmen: Willem J. Remme, Rotterdam-Rhoon, Karl Swedberg, Göteborg.

Members: John Cleland, Hull; A. W. Hoes, Utrecht (General Practice); Attilio Gavazzi, Bergamo (WG Myocardial and Pericardial diseases); Henry Dargie, Glasgow; Helmut Drexler, Hannover; Ferenc Follath, Zurich (European Federation of Internal Medicine); A. Haverich, Hannover (WG on Cardiovascular Surgery); Tina Jaarsma, Den Haag (WG on Cardiovascular Nursing); Jerczy Korewicki, Warsaw; Michel Komajda, Paris; Cecilia Linde, Stockholm (WG on Pacing); Jose Lopez-Sendon, Madrid; Luc Pierard, Liège (WG on Echocardiography); Markku Nieminen, Helsinki; Samuel Levy, Marseille (WG on Arrhythmia); Luigi Tavazzi, Pavia; Pavlos Toutouzas, Athens.

## Appendix 2

### Reviewers

O. Alfieri, Milan; J. P. Bassand, Besançon; M. Böhm, Saarbücken; M. Halinen, Kuopio; R. Hobbs, Birmingham; J. Hradec, Prague; W. Klein, Graz; J. Kobberling, Wuppertal; J. McMurray, Glasgow; A. Oto, Ankara; P. Poole-Wilson, London; L. Rydén, Stockholm.

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